NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Roche Products Ltd
   - Multiple Sclerosis Society
   - Multiple Sclerosis Trust
   - Association of British Neurologists

3. **Comments on the Appraisal Consultation Document from experts:**
   - Yvonne Pettigrew, Patient Expert, nominated by the Multiple Sclerosis Trust

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Additional evidence provided by Roche Products Ltd**

6. **Evidence Review Group review of additional evidence** prepared by Warwick Evidence

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Ocrelizumab for treating primary progressive multiple sclerosis

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1	Consultee	Roche Products Ltd; hereinafter "Roche"	Roche appreciates the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for *'Ocrelizumab for treating primary progressive multiple sclerosis [ID938]'*. While disappointed that the committee was unable to recommend ocrelizumab in the ACD and did not see a need for the proposed Managed Access Agreement, Roche is committed to exploring all options to ensure ocrelizumab is made available to NHS patients. In the spirit of trying to find a solution we have proposed an alternative commercial offer; however, pending agreement on its implementation we are as yet unable to present it to the Committee for consideration. Given the significant unmet need - with a complete lack of effective treatments that modify the course of the disease - and the current inequity between people with different forms of MS, we ask for greater flexibility to be applied that would allow consideration of the proposed commercial arrangement and demonstration of plausible cost-effectiveness. We therefore request that all relevant stakeholders (including NICE, NHSE and Roche) meet to discuss potential pragmatic mechanisms that would permit access to this innovative medicine for people with early PPMS. Roche has submitted an appendix with new evidence from the open label extension (OLE) period of the pivotal phase 3 ORATORIO study. These new data were not available until after the first appraisal committee meeting, and address the uncertainty around the size and durability of treatment effect, as raised by the committee in the ACD. The OLE data represent the longest duration of continuous data available for ocrelizumab (6 ½ years of follow-up). In addition, Roche has submitted an appendix with results of a revised base case using the following modelling assumptions preferred by the committee: • CDP-24 used as the measure for disability progression • Cost and disutilities of relapses included	Thank you for your comment. The committee considered both the revised base-case and the submitted data from the open label extension study. The FAD has been amended to reflect this – see sections 3.8, 3.9, 3.10, 3.12, 3.13, 3.14, 3.16 and 3.17. NICE are open to engaging with the company and NHS England. However, as clarified during the committee meeting the committee can only consider prices agreed with NHS England (see section 4.6 of the TA process guide). NHS England confirmed to NICE that it cannot consider the commercial arrangement proposed by the company. So at its second meeting, the committee could only consider ocrelizumab at the price for the patient access scheme for relapsing remitting multiple sclerosis. Further, the committee heard from NHS England that they can only consider the type of arrangement proposed by the company in limited, specified circumstances, which do not apply to this case.

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			• Risk of progressive multifocal leukoencephalopathy (PML) for ocrelizumab included (using data from rituximab in rheumatoid arthritis as proxy, similar to the approach in the recent NICE appraisal for ocrelizumab in relapsing MS, ID937) • Utility decrement for fatigue excluded • 50% waning after 10 years included (uncertainty was highlighted by the committee, concluding that true waning likely lies between an assumption of no waning and an assumption of 50% waning after 5 years. Based on the durability of effect observed in OLE data, we propose that waning is assumed to start after 10 years [in line with recent RRMS MTA TA527], see below) • UK MS Survey used as the source of EDSS costs (in line with committee's conclusion that EDSS costs are the same in RRMS and PPMS, similar to the approach used in the recent NICE appraisal for ocrelizumab in relapsing MS, ID937) • Stopping rule of EDSS ≥7 used (in line with Roche's understanding of the ACD, uncertainty highlighted by the committee) • 50% increased stopping rates after 5 years used, as proposed by the ERG (uncertainty highlighted by the committee) However, Roche believe that several conclusions in the ACD are not a reasonable and fair interpretation of the evidence and encourage the committee to reconsider its conclusions. The responses below address these themes in turn: 1. Effect size and durability 2. Utility decrements for upper limb dysfunction 3. Health state utility values 4. Treatment waning, treatment duration, and stopping rules 5. MSBase registry data 6. Proposed commercial arrangement The revised base case analysis presented in the appendix therefore includes the following modelling assumptions preferred by Roche: • CDP-24 effect size from crossover adjustment of OLE (new evidence) • Health state utility values from ORATORIO study used to reflect the population with early PPMS with inflammatory activity	

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			• Utility decrements for upper limb impairment included The impact of some of these assumptions and inputs is explored further in scenario analyses (see appendix).	
2	Consultee	Roche	**Ocrelizumab treatment effect** The ACD states in 3.22 that *'Ocrelizumab slows disability progression compared with placebo, although the size and duration of the effect are uncertain.'* Roche would like to make the committee aware of new data supporting the long-term efficacy of ocrelizumab in PPMS, which provides additional evidence of the treatment duration and effect size. Patients completing the phase III ORATORIO study could enter an OLE period following unblinding of study centres, which started when the study was ascertained to be positive (initiated 12th Oct 2015). Upon completion of the ORATORIO double-blind placebo-controlled period, patients remained blinded and on-treatment as originally assigned for an additional extended controlled treatment period (ECP) ranging from the clinical cut-off date (24th July 2015) until the first dose of OLE, and was completed when the last patient entered the OLE (27th April 2016). The most recent data cut-off from the OLE extends to Week 336 (5th February 2018) (i.e. nearly 6 ½ years of follow-up). Upon entering the OLE, patients previously receiving placebo switched onto ocrelizumab. To estimate comparative long-term treatment effect versus placebo during the OLE, crossover was adjusted using the Rank Preserving Structural Failure Time (RPSFT) model. This methodology is endorsed by the NICE DSU document TSD16 (1) and has been employed in many previous oncology NICE appraisals as well as a recent RRMS appraisal (2) to estimate treatment effect during OLE periods. RPSFT produces a counterfactual data set, adjusting the survival estimate in the presence of treatment switching in order to provide an estimate of the survival times that would have been observed in the absence of switching. This type of crossover adjustment method assumes a common treatment effect, whereby the treatment effect received by those switching from placebo to ocrelizumab is assumed to be the same as the treatment effect received by those initially randomised to ocrelizumab. Clinical advice was sought at a recent advisory board organised by Roche to assess the validity of this assumption. Clinical experts considered this assumption to be valid as switching upon entering the OLE was not dependent on progression and hence the risk of progression can be considered	Thank you for your comment. The committee considered data from the open label extension study provided. It noted that using unblinded data increased the risk of performance and detection bias. In addition, unlike data from the double-blind period alone, the treatment effect incorporating the open label extension data was larger for CDP-24 than for CDP-12 which appeared counterintuitive. The committee concluded that using data from the open-label extension increased rather than decreased uncertainty about the size of the treatment effect. It further concluded that the model should have incorporated data from only the double-blind period of the ORATORIO trial so it did not consider the methods used to adjust for cross-over. The FAD has been amended to reflect this – see FAD section 3.8.

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			equal between the time of randomisation and time of entering OLE/switching. An alternative method of crossover adjustment, inverse probability of censoring weighted (IPCW), necessitates the use of longitudinal data on covariates and patient characteristics which predict treatment switching and prognosis. This information was not collected in ORATORIO OLE and therefore an IPCW model cannot be applied to the dataset to adjust for crossover. For the above reasons we therefore believe the RPSFT crossover adjustment is a valid method to estimate the long-term treatment effect of ocrelizumab. The robustness of the crossover adjustment was assessed in sensitivity analysis and the consistency of OLE results was assessed by comparing results across different disability outcomes (CDP-12 and 9-HPT). The risk of selection bias was considered minimal in the OLE study, as very few patients chose not to enter the OLE study (see Appendix). The most common reason recorded for not entering the OLE was 'completed study'. In addition, no pattern for reasons of censoring could be discerned between pre- and post-OLE entry in the cohort of patients switching from placebo to ocrelizumab. <u>New evidence from OLE study in MRI active population</u> Analysis of the OLE data over 6 years indicated that the treatment effect size for ocrelizumab in the MRI active population further increases past the initial controlled treatment period. This increased treatment effect was consistently observed when a different disability outcome was assessed, CDP-12 (see Appendix). The size of treatment effect on upper limb function remained largely stable over time. Sensitivity analysis indicates that the crossover-adjusted effect size is relatively insensitive to different analysis methods and assumptions (see Appendix). The phenomenon of a lag time before reaching maximal treatment effect size on disability outcome measures has been observed in other trials of anti-inflammatory DMTs in progressive forms of MS (3). A biological mechanism has been proposed to explain the observed therapeutic lag of effect on disability accumulation with anti-inflammatory therapies, such as ocrelizumab, in progressive forms of MS. This lag may be explained by the delayed neurodegeneration induced by prior inflammation and can be compounded where there is limited neuronal reserve left to compensate for this damage (4). The low neuronal reserve for lower extremity function may lead to a long delay between anti-inflammatory intervention and therapeutic benefit on EDSS progression. Therefore, it may take several years for	

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			the effect of an anti-inflammatory DMT on lower limb disability to become clinically apparent. The increased treatment effect size for ocrelizumab with regards to CDP-24 and CDP-12 appears to follow the pattern predicted by this hypothesis (see Appendix). Furthermore, as upper limbs are typically affected at a later stage of the disease than lower limbs (proposed to be explained by the decreased likelihood of a lesion in shorter length central axons projecting towards the upper limbs vs. lower limbs – known as the length-dependent MS axonopathy hypothesis, as well as the observation that the region of the spinal cord most commonly damaged is below that which serves the upper limbs), it is anticipated that they will have accrued less damage and retain higher reserve capacity. Therefore, not only is the subsequent clinically apparent disability less significant but also the retained reserve can compensate for any damage that does occur (4-8). Consistent with this, the maximum treatment effect of ocrelizumab on upper limb function is achieved after a shorter period of time i.e. without a significant lag, as more of the effect is acting on current or recent inflammation with less delayed neurodegeneration to effect and therefore consistent with higher neuronal reserve. Consequently, the treatment effect size for 9-HPT remains constant through the OLE (see appendix).	
3	Consultee	Roche	**Utility decrements for upper limb dysfunction** The committee concluded in 3.15 of the ACD that it is not appropriate to include additional utility decrements for upper limb dysfunction. The reasons given were the following: • *The ERG highlighted that previous appraisals for multiple sclerosis had not used specific utility decrements for symptoms.* • *The clinical experts commented that upper limb function are equally important for people with relapsing–remitting multiple sclerosis.* Roche is particularly concerned by this conclusion and believe it contradicts section 3.2 of the ACD which recognises the pivotal role of upper limb function in maintaining patients' independence. We would like to reiterate the importance of upper limb function to patients with MS, and refer to a recent survey which indicated that a majority of patients with MS in the UK (88%) considered upper limb function to be more important than lower limb function (9). Upper limb dysfunction is not a symptom, instead it is an important component of multi-dimensional disability in PPMS that is not adequately captured by EDSS. Manual dexterity is an important predictor of overall activity and participation within the community – upper limb dysfunction in MS contributes to a reduced ability to perform activities of daily living, resulting in decreased independence and quality of	Thank you for your comment. The committee noted that upper limb function was an exploratory endpoint in ORATORIO and questioned why the company had selected this outcome to include in the model rather than the many other exploratory endpoints measured. The committee heard from the ERG that the measure of upper limb function used in ORATORIO (changes in time to complete the 9-hole peg test) may not reflect changes in upper limb function that matter to people, such as reduced ability to wash, dress and feed themselves. The committee objected to using chosen selected exploratory endpoints in the modelling without considering the risk of false-positive findings. The committee still considered at its second meeting that including decrements for upper limb function, decreasing utilities as people progressed through EDSS states, and carer disutilities likely overestimated the effect of ocrelizumab on slowing disability progression. It concluded that it was inappropriate to include utility decrements from upper limb dysfunction in the economic model. Section 3.16 of the FAD has been amended to reflect this.

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			life [58]. Dysfunctions of the upper extremities occur in at least 66% of people with MS, and approximately 44% experience problems with activities of daily living [59]. Furthermore, utility decrements for upper limb dysfunction should not be excluded from the model because they have not been incorporated in economic models of RRMS to date. Our understanding of all forms of MS continues to evolve and there is a growing appreciation of the impact of upper limb function on patients' independence and health-related quality of life (HRQoL). Therefore, we urge the committee to permit advancements in the understanding of a disease to be acknowledged and reflected in this appraisal. Whilst we agree that maintaining upper limb function is important for both people with RRMS and those with PPMS, it is more ***relevant*** for people with PPMS. This is due to the longer time to diagnosis for people with PPMS, and subsequently these patients often already have significant lower limb disability and are closer to being in a wheelchair at the point when treatment can potentially be initiated compared to those with RRMS. Consequently, preserving upper limb function is a more relevant treatment goal for people with PPMS. The non-linearity of the EDSS scale means that it is less sensitive to increasing disability at later stages of disease. Conversely, the 9-HPT provides greater precision, i.e. it captures upper limb disability progression occurring between higher EDSS states. Therefore, measurements of the impairment of upper limb functions give important additional information about patients' level of disability affecting their HRQoL, that is not adequately captured by EDSS alone. The impact of upper limb impairment on patients' HRQoL was quantified by evidence from the ORATORIO study in PPMS. Multivariate regression analysis of EQ-5D data collected in the trial indicated that upper limb dysfunction affected HRQoL ***independent*** of EDSS state. After controlling for EDSS at later stages of disease (EDSS ≥5), upper limb impairment led to a reduction in utility of −0.064 (p=0.013). The regression analysis followed a similar approach to Orme et al (2007) (10) which reported utility decrements for relapses and disease type (RRMS, SPMS, PPMS) and has been used in previous NICE appraisals in RRMS. The latest study published by the same research team reported utility decrements for fatigue and cognitive impairment independent of EDSS in patients with MS (11). Upper limb function was not measured in this study. The ORATORIO trial evidence provides a unique dataset of patients with PPMS in	

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			which upper limb function was measured (using 9-HPT) alongside patient-reported HRQoL (using EQ-5D), and is therefore the first study to demonstrate the independent effect of upper limb dysfunction on HRQoL in patients with MS (12). For all these reasons, we strongly believe that the importance of upper limb function should be translated into QALYs and that it is therefore appropriate to include utility decrements of upper limb dysfunction in the economic model, and we encourage the committee to reconsider their conclusion.	
4	Consultee	Roche	**Health state utility values** The committee concluded in 3.14 of the ACD that utility values from Orme et al (2007) were preferred. The reasons given for this are the following: • *The committee noted that the population that its recommendations would apply to would include people aged over 55 years who are not represented in ORATORIO.* • *also preferred using utility values from a single source, rather than using different sources for different EDSS states.* Roche does not agree with this conclusion and believe it needs contextualisation. The marketing authorisation for ocrelizumab is in early PPMS with inflammatory activity. As shown in Figure 14 in our response to clarification questions, evidence from the ORATORIO study demonstrated there is a trend of decreasing inflammatory activity with age. This is likely explained by the underlying pathology of the disease course in PPMS shifting from an inflammatory to a primarily neurodegenerative process. As such, patients with inflammatory activity tend to be younger and we would not expect many patients over 55 years to be eligible for treatment with ocrelizumab. The utility values described in Orme et al (2007) were elicited from people with PPMS, not specifically early PPMS with inflammatory activity. The average age in Orme et al (2007) (51 years for the full cohort of patients with MS, average age for the sub-cohort with PPMS unknown) was considerably higher than that in the ORATORIO study (44 years). Based on the trend observed in ORATORIO, it can be speculated that not many patients with PPMS in Orme et al (2007) had inflammatory activity. As such, the characteristics of this patient cohort may be fundamentally different from the one that matches eligibility for treatment with ocrelizumab. The utility values from the ORATORIO study are therefore more appropriate to apply in the economic model as these reflect the population that the NICE	Thank you for your comment. The committee acknowledged that it is appropriate to use utility values from the ORATORIO study for EDSS states, supplemented by values from the literature. The FAD has been amended to reflect this – see FAD section 3.15.

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			recommendation would apply to. In addition, in previous appraisals in RRMS the committee preferred using utility values from clinical trials supplemented with Orme et al (2007) for the highest EDSS states not included in the trials, and we see no reason for a different approach in PPMS. Although it is not ideal to mix different sources for utilities, the trial should be considered the best available evidence to reflect people with early PPMS with inflammatory activity.	
5	Consultee	Roche	**Treatment waning, treatment duration, and stopping rules** The committee concluded in 3.11 of the ACD that *'treatment efficacy may wane over time with ocrelizumab, but the absolute rate of waning is uncertain. The committee concluded that the company's assumption of no waning of treatment effect was too optimistic, but that the ERG's approach may be too pessimistic. It concluded that the true waning of treatment effect is likely to lie between these 2 approaches.'* Furthermore, the committee states in 3.12 of the ACD that *'including both stopping and, separately, waning in the ERG's base case may have overestimated the rate of stopping treatment. It concludes that there is considerable uncertainty about how long people would continue to take ocrelizumab.'* Roche would like to refer the committee to the latest analysis from the OLE study (see above and in the appendix) which demonstrates a sustained effect during 6 ½ years of follow-up. OLE data supports lack of a waning effect during this period, and therefore we believe the ERG scenario of assuming a 50% drop in efficacy after 5 years to be implausible. Furthermore, ocrelizumab is associated with very low incidence of anti-drug antibodies (see company submission). This is due to the relatively low immunogenicity profile associated with humanised antibodies. The presence of anti-drug antibodies correlates with reduced efficacy of other DMTs in MS (13-18). As such, the negligible proportion of patients treated with ocrelizumab developing neutralising antibodies suggests they cannot be a source of treatment waning for ocrelizumab. Waning may be hypothesised to occur when the underlying disease course is no longer driven by inflammatory processes. There is a lack of evidence about when this occurs in PPMS, and cannot be monitored by MRI whilst on treatment because ocrelizumab causes near-complete (>95%) suppression of MRI activity. As such, it is important for clinicians and patients to monitor clinical events of progression on multi-dimensional aspects of disability and to agree when to stop treatment. Roche	Thank you for your comment. The committee considered the data from the open label extension study. It concluded that the company's original assumption of no waning of treatment effect was too optimistic but that, acknowledging the issues of open-label extensions (discussed in section 3.8 of the FAD), the ERG's revised approach (assuming treatment waning from 7 years) may still be too pessimistic. It concluded that the true waning of treatment effect is likely to lie between the company's and ERG's updated approaches, and that exploring assumptions of treatment waning between 7 years and 10 years is reasonable. Section 3.12 of the FAD has been updated to reflect this. The committee further heard from the ERG that the company's revised base case approach did not match the ERG's, because the ERG preferred to link treatment waning (by applying a reduced treatment effect) with an increased rate of stopping treatment. The committee considered that this approach may be too conservative because people remaining on the drug would be expected to show a good response, and would potentially not experience a reduced treatment effect. It concluded that there is considerable uncertainty about how long people would continue to take ocrelizumab, but that the ERG's base case is likely to have overestimated the rate of stopping treatment. Section 3.13 of the FAD has been amended to reflect this.

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			believes that a consensus of the clinical community about stopping criteria could allow management of patients' expectations. We agree with the committee's conclusion that including both stopping and waning may be considered double counting. The committee concluded in the ocrelizumab in RRMS appraisal (ID937) that stopping rates could be considered proxies for waning rates, and we believe this principle to be relevant in PPMS as well. We do not agree with the committee's assertion that including both waning and stopping rates may have overestimated the rate of stopping. This implies that more patients would continue treatment despite the presence of waning. We do not believe this to be plausible and would argue instead that including both stopping and waning rates likely overestimates the rate of waning, as patients would be expected to stop if they no longer derive the expected benefit from treatment. Despite the above concerns about double counting, we propose in our revised base case for PPMS a waning effect of 50% after 10 years. We believe this to be conservative as our OLE study provides evidence of sustained long-term effect. However, this waning assumption is in line with the one used by NICE in the recent MTA for beta-interferons and glatiramer acetate (2). The impact of assuming no waning or not applying increased stopping rates is explored in a scenario analysis.	
6	Consultee	Roche	**Natural history of early PPMS** The ACD states in 3.10 that '*The clinical experts commented that a lot of data in the MSBase registry come from Eastern Europe, where the definition of primary progressive multiple sclerosis may differ from the UK. The committee concluded that it had concerns about using data from the MSBase registry to inform baseline transitions between EDSS states in the absence of treatment in the company's model, and considered that its use was associated with uncertainty*.' Roche would like to clarify that the MSBase analysis was a bespoke project for this submission. The cohort used to derive transition probabilities matches the ORATORIO inclusion criteria to mimic early PPMS, and is not the full PPMS dataset in the MSBase registry. Canada, Spain, Italy, Netherlands and Australia are the top 5 countries that contributed to this analysis and accounted for 80% of the early PPMS analysis set (data on file). These countries' healthcare systems are similar to the UK and are expected to adhere to similar definitions of PPMS diagnosis and treatment. We therefore expect the MSBase PPMS cohort to not significantly differ from the UK PPMS population, and for the transition probabilities	Thank you for your comment. The committee acknowledged that it was appropriate to use the MSBase registry to inform baseline transitions between EDSS states in the absence of treatment in the company's model. Section 3.11 of the FAD has been amended to reflect this.

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			in the model to be appropriate. The MSBase registry currently represents the best available evidence of natural history in PPMS. As explained in the company submission, other registries were contacted but their datasets did not contain the necessary depth and completeness in PPMS to derive transition probabilities for the economic model. Likewise, the placebo arm of the ORATORIO study contained fewer data points (fewer patients and shorter follow up duration than the registry), which would have introduced more uncertainty. As exemplified by previous NICE appraisals in RRMS, registry data is preferable to trial data for deriving long-term natural history.	
7	Consultee	Roche	**Proposed commercial arrangement** The committee noted in 3.17 of the ACD that '*the company presented a proposal for a commercial arrangement. It stated that this would provide ocrelizumab to the NHS at a reduced price (which is commercial in confidence) until an ongoing trial finishes'*. Roche would like to clarify that the proposed commercial arrangement would be expected to apply not only during the period of data collection but indefinitely, unless a future NICE re-review of this appraisal warrants a review of the arrangement with the NHS.	Thank you for your comment.
8	Consultee	Roche	An updated base case is provided in response to this ACD which reflects many of the committee's preferences, as discussed above. However, inputs for health state utility values and inclusion of utility decrements for upper limb dysfunction are based on company's preferences, as explained in earlier sections of this response. A number of scenario analyses have been conducted to explore the impact of uncertainty around a number of modelling assumptions. Full details can be found in the Roche ACD response appendix; however, a summary is provided below. <u>New base case analysis</u> The updated base case results in a QALY gain of [redacted] with ocrelizumab treatment, compared with [redacted] QALYs with BSC. The resulting incremental ICER for ocrelizumab compared with BSC is £62,766 based on the approved PAS for ocrelizumab, without consideration of the proposed commercial offer. <u>New scenario analyses</u> Additional scenario analyses explored the impact of different parameters and inputs. The results were particularly sensitive to the source of efficacy (i.e. double blind trial period only, or including open label extension period). In addition, source of health state utilities values and impact of upper limb function were key drivers of	Thank you for your comment. The committee considered the revised base case and the FAD has been amended to reflect this – see sections 3.9, 3.10, 3.12, 3.13, 3.14, 3.16 and 3.17. The committee considered the unmet need for disease-modifying treatments for this condition and the innovative nature of ocrelizumab for primary progressive multiple sclerosis alongside the evidence on clinical and cost-effectiveness – see FAD sections 3.1 and 3.18. NICE are open to engaging with the company and NHS England. However, as clarified during the committee meeting the committee can only consider prices agreed with NHS England (see section 4.6 of the TA process guide). NHS England confirmed to NICE that it cannot consider the commercial arrangement proposed by the company. So at its second meeting, the committee could only consider ocrelizumab at the price for the patient access scheme for relapsing remitting multiple sclerosis.

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			the model. Finally, the results were sensitive to clinical uncertainties highlighted by the committee in the ACD, i.e. waning assumption and treatment duration. We ask the committee to consider the lack of treatment options in PPMS, the inequity between people with different forms of MS, and the innovative nature of ocrelizumab, as highlighted in the ACD. We hope that further discussions are enabled with all relevant stakeholders (including NICE, NHSE and Roche) to discuss potential solutions to allow Roche's commercial offer to be taken into consideration. Together with the revised base case assumptions, we believe that greater flexibility around implementation of commercial arrangements would enable people with early PPMS with inflammatory activity to have access to ocrelizumab in the NHS.	Further, the committee heard from NHS England that they can only consider the type of arrangement proposed by the company in limited, specified circumstances, which do not apply to this case.
9	Consultee	Association of British Neurologists	We are disappointed that Ocrelizumab will not be available at current cost. Ocrelizumab is the first licensed medicine for primary progressive multiple sclerosis and meets an unmet need. Slowing disability progression will have a noticeable effect on disability progression in upper limbs as well as walking. There will be reduced costs from need for Care, need for aids and benefits. More people may be able to stay in employment.	Thank you for your comment. The committee noted the unmet need for disease-modifying treatments for this condition, and the substantial effect that this has on the lives of people with the condition and their families. The committee also noted that slowing disability progression and preserving upper limb function would allow people to continue working, engage in everyday activities and care for themselves for longer (see sections 3.1 and 3.2 in the FAD for further details of committee considerations).
10	Consultee	Association of British Neurologists	Although definitions of "early" and of "active " disease on MRI pose problems with the increase need fro MRI and gadolinium use practical definitions and use of other sequences such as diffusion weighted change may mitigate this burden.	Thank you for your comment.
11	Consultee	Association of British Neurologists	The risk of PML with Ocrelizumab is most likely to be similar to Ritixumab, Clifford et al Arch Neurol 68(9) 1156-1164 form 2011 reported only 4 cases in 129,000 people treated of Rheumatoid arthritis, estimating a risk of 1 in 25,000.	Thank you for your comment.
12	Consultee	Association of British Neurologists	Facilities for administration and safety monitoring of Monoclonal antibodies already exist in MS centres due to use in relapsing disease, although increased need for MS Nurses, Infusion capacity and access to Neurology as well as MRI is to be anticipated.	Thank you for your comment.
13	Consultee	MS Society	**Unmet treatment need** Primary progressive MS represents a huge unmet need in MS treatment with no disease modifying treatments currently available on the NHS. People affected by primary progressive MS are, understandably, feeling incredibly let down by NICE's appraisal consultation document recommendation. There are now 13 licensed disease modifying treatments on the NHS for people with relapsing MS offering a range of efficacy levels, side effects and ways to take a treatment. Yet ocrelizumab is the only licensed disease modifying treatment option	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis, and considered the unmet need for disease-modifying treatments for this condition (see section 3.1 of the FAD).The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.

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			for primary progressive MS. People have watched and waited while licensed treatments for relapsing MS have rapidly increased and becoming more effective and easier to take, pinning their hopes on ocrelizumab as potentially their first NHS treatment. While NICE have acknowledged the importance of ocrelizumab and the concerns of people with primary progressive MS they have not gone as far as to recommend that it is used on the NHS. It is vitally important to people affected by primary progressive MS that ocrelizumab is approved by NICE for as many people as possible.	
14	Consultee	MS Society	**The importance of factoring in upper limb function** For primary progressive MS where relapse rate is less of an indicator for clinical effectiveness it is important to consider any available evidence of treatment effect. People with primary progressive MS have written to us of the importance of maintaining as high a degree of independence as possible. As a person's disability progresses the importance of upper limb function increases as people become increasingly dependent on it to maintain a level of mobility and independence. Common measures of disability in MS including EDSS have been described as "insensitive to change at the higher end" by the Nuffield Trust in a recent report commissioned by the MS Society[1], which means disability progression such as upper-limb function may be undervalued in terms of utility decrement. At the committee meeting the clinical experts were asked if upper limb function should be looked at as a separate utility decrement when it is not usually in relapsing MS appraisals. Within this context the clinical experts agreed it shouldn't be treated as more important in people with primary progressive than relapsing MS, and the issue was not revisited by the committee. If the committee had asked the clinical experts whether greater importance should be placed on upper limb function in appraisals generally they would have likely given an affirmative answer. Trials for relapsing MS have focused predominantly on annual relapse rate as a primary end outcome but the importance of the 9 hole peg test in MS clinical trials is only now being fully acknowledged as more research aims to assess the impact of DMTs on upper limb function. This is something that the EMA have already accepted in principle.[2]	Thank you for your comment. The committee noted the importance of preserving upper limb function for people with multiple sclerosis (see section 3.2 of the FAD) and considered evidence submitted by the company relating to upper limb function from the ORATORIO trial and an open-label extension of the trial. The committee concluded that it is not appropriate to include additional utility decrements for upper limb dysfunction in the economic model. This was because upper limb function was an exploratory endpoint in the ORATORIO trial and the committee questioned why the company had selected this outcome to include in the model rather than the many other exploratory endpoints measured. The committee also heard from the ERG that the measure of upper limb function used in ORATORIO (changes in time to complete the 9-hole peg test) may not reflect changes in upper limb function that matter to people, such as reduced ability to wash, dress and feed themselves. It further considered that including decrements for upper limb function, decreasing utilities as people progressed through EDSS states, and carer disutilities likely overestimated the effect of ocrelizumab on slowing disability progression. Section 3.16 of the FAD has been amended to reflect this. In addition, the committee concluded that ocrelizumab was not cost effective for treating primary progressive multiple sclerosis at the patient access scheme price even in the company's base case analysis - which

[1] Castle-Clarke S, Curry N, Dorning H and Wetherly L (2018) Improving care for people with MS: the potential of data and technology. MS Society. Report www.nuffieldtrust.org.uk/research/improving-care-for-people-with-ms-the-potential-of-data-and-technology

[2] https://pharmaphorum.com/news/ms-drugs-needed-preserve-hand-function/

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			NICE should consider all evidence which has been submitted to them when modelling ocrelizumab's effectiveness in primary progressive MS and in particular adding utility decrements to reflect the full importance of upper-limb function in MS. NICE acknowledging the importance of capturing upper limb function in this way would show strong leadership and ensure that more people with MS are able to take part in clinical trials in the future.	included additional utility decrements for upper limb dysfunction (see section 3.17 of the FAD).
15	Consultee	MS Society	**Stopping criteria** Currently treatments for MS in England are stopped when someone reaches EDSS 7.0 and require the use of a wheelchair. This is due to the clinical trial eligibility not including wheelchair users. Many clinicians, having witnessed their patients relapsing when taken of treatment, are concerned over the impact the stopping criteria is having. As set out above the use of EDSS 7.0 as a stopping criteria reflects the undue prominence given to mobility over upper limb function in previous clinical trials, rather than specific evidence that DMTs are not effective beyond this point of progression. We therefore agree with the clinical expert that continuing treatment to an EDSS stage of 8.0 (or potentially 8.5, which is the point at which upper-limb function has deteriorated) is more appropriate. This broadly maps onto the trial population in the sense that starting criteria went up to 6.5 and the definition of clinical progress was an increase of 1 point on the EDSS scale (but some people saw greater increases).	Thank you for your comment. The committee considered a stopping rule of EDSS 8.0 for ocrelizumab for primary progressive multiple sclerosis, including your response to the question on this asked at consultation. Section 3.14 of the FAD has been updated to reflect this. However, the committee concluded that, although there is considerable uncertainty about an appropriate stopping rule, it had not been presented with any evidence to support a stopping rule that differed by type of multiple sclerosis (see section 3.14 of the FAD).
16	Consultee	MS Society	**Importance of innovation** The appraisal consultation document acknowledges that ocrelizumab is an innovative new treatment which marks a 'step change' in treatment for primary progressive MS. This needs to be taken into full consideration when factoring in the levels of uncertainty within the models analysed by NICE. The MS Society would like to see steps taken to ensure that ocrelizumab is made available to as many people eligible as possible. We would like to see NICE and Roche work together to reach a compromise which allows people with primary progressive MS to access this innovative new treatment.	Thank you for your comment. As noted in the comment the committee considered that ocrelizumab is an innovative treatment for primary progressive multiple sclerosis (section 3.18 of the FAD). The committee took the innovative nature of the treatment into consideration in its decision-making alongside the evidence on clinical and cost-effectiveness. NICE are open to engaging with the company and NHS England. However, as clarified during the committee meeting the committee can only consider prices agreed with NHS England (see section 4.6 of the TA process guide). NHS England confirmed to NICE that it cannot consider the commercial arrangement proposed by the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
				company. So at its second meeting, the committee could only consider ocrelizumab at the price for the patient access scheme for relapsing remitting multiple sclerosis. Further, the committee heard from NHS England that they can only consider the type of arrangement proposed by the company in limited, specified circumstances, which do not apply to this case.
17	Consultee	MS Society	**Wider impact on carers/societal benefits** For those who are still in work the fear of having to retire early and to seek financial support is a particular worry. A point raised by many people with MS in support of our previous submission as to why they want ocrelizumab was to help keep them providing for themselves and their family. As primary progressive MS is typically diagnosed in people in their forties, many people have young children. We have heard from numerous people and their carers who speak of how difficult they find it to be dependent on their family to help care for both them and their children. People with MS often need support from family and/or friends to help them to manage the impact of having MS, to help them remain independent and lead a fuller life. This includes support with everyday tasks like washing and dressing and getting out and about. As disability progresses the need for this support increases and the impact on carers can be greater. Recent research by the MS Society showed that the proportion of people with MS who received care, support or assistance from a friend or family member had increased from 71% to 85% from 2013 to 2016.[3] If people had access to ocrelizumab and were able to decrease the progression of disability there would be less need to rely on support from carers. This was brought up frequently by people who wrote to us in support of this submission, many of whom are concerned about the impact their MS has on their family.	Thank you for your comment. The committee considered that many people with primary progressive multiple sclerosis eventually need support and care from family members or friends, and that the condition can substantially affect the lives of people with the condition and their families. Furthermore, slowing disability progression and preserving upper limb function allows people to continue working, engage in everyday activities and self-care for longer (see sections 3.1 and 3.2 of the FAD for more detail on committee considerations). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
18	Consultee	MS Society	**Hope and the impact on mental health** It has been estimated that up to 50% of people with MS experience clinical depression which can have profound effects on a person's quality of life requiring medication and other interventions to treat. The first treatment of its kind, ocrelizumb offers people hope for the future of their condition where it was previously lacking. The impact that hope and optimism for the future can have on	Thank you for your comment. The committee considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer

[3] Wallace, L., Cavander- Attwood, F., Redfern-Todts, D. Social care and the MS community in England 2016

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			mental health is well documented and should be considered as an extra factor by the committee.[4] The negative impact on mental health that being diagnosed with an untreatable progressive condition has cannot be overstated. Some people have commented to us that they hope ocrelizumab will help slow their progression until more effective treatments are established. Other people hope that ocrelizumab could be even more effective than the trials have indicated so far, giving them a chance to get some mobility back so that they can again engage in everyday activities, such as walking to the shops or even to the bathroom without difficulty. Others have more modest hopes that ocrelizumab will slow their disability progression allowing them to stay active for longer so that they can keep providing for their family. For many others the thought of being able to achieve important milestones in life that they currently feel will be impossible is inspiring. As we highlighted in our previous submission people spoke of "maybe being able to walk my daughter down the aisle one day", or about taking "my son to football matches without worrying how far I would have to walk". People with progressive MS have seen the innovation and progress that has been achieved in treating relapsing MS since beta interferons and glatiramer acetate were first conditionally approved in the risk sharing scheme and they hope that an approval for ocrelizumab could lead to similar benefits.	perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
19	Consultee	Multiple Sclerosis Trust	The MS Trust is extremely disappointed that NICE is unable to recommend ocrelizumab as an NHS treatment for early primary progressive MS with imaging features characteristic of inflammatory activity.	Thank you for your comment.
20	Consultee	Multiple Sclerosis Trust	**Huge unmet need** While we recognise the difficulties posed by this appraisal, we wish to emphasise the huge unmet need for a treatment which will slow down progression in primary progressive MS (PPMS). Our announcement of NICE's initial decision to reject ocrelizumab for PPMS was greeted by bitter disappointment from our supporters. Before preparing our appraisal submission to the committee, we conducted a survey to gather the views of those affected by PPMS. We received nearly 500 responses (31 January – 14 February 2018) from people with PPMS, their families and specialist MS health professionals. Time and again respondents to our survey commented that there is currently no treatment to delay the progression of PPMS, nothing that can change the prognosis of their condition. Many people are doing all that they can to minimise the impact of	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis, and considered the unmet need for disease-modifying treatments for this condition (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness.

[4] Conversano, Ciro et al. "Optimism and Its Impact on Mental and Physical Well-Being." *Clinical Practice and Epidemiology in Mental Health : CP & EMH* 6 (2010): 25–29. *PMC*. Web. 16 July 2018.

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			PPMS, but they are all too aware that there is nothing that will slow down the progression of their disease. The overwhelming majority of people with PPMS are delighted that there is, at last, potential to slow down the progression of their condition; over the years as the number of treatments available for relapsing MS have grown, people with progressive MS have felt that their needs have been forgotten. Many respondents to our survey recognised that their PPMS may be too advanced to gain a benefit, but believed others should be given the opportunity to take a medication that would improve their prognosis and quality of life. The benefits of slowing down progression are seen as maintaining mobility and independence for longer, allowing people to continue to work for longer, and saving costs for the NHS in the long term by preventing progression and the need for MS services and social care.	
21	Consultee	Multiple Sclerosis Trust	**Primary progressive MS different to relapsing remitting MS** Throughout the ACD, reference is made to appraisals for relapsing remitting MS. We wish to state very clearly that the lived experience of PPMS is very different to relapsing MS. We urge the committee to recognise the significant differences between PPMS and relapsing MS and how they affect someone's daily life, and their outlook for the future. We are very concerned that these differences are properly and fairly reflected in the calculations of cost effectiveness and modelling which are so critical to the outcome of this appraisal. In particular, we note that discussions around the most appropriate utility values for modelling purposes (3.14, page 13) propose using those from Orme et al which groups the different types of MS together. The data from Hawton and Green, 2016 separates out health state utility values (HSUVs) by type of MS – according to both the EQ-5D and the SF-6D, HSUVs were lower for those with progressive MS than for those with relapsing MS, implying that PPMS and secondary progressive MS have a greater impact on health-related quality of life. Can the committee, ERG and manufacturer confirm that the utility values from Orme adequately reflect this difference? In PPMS, disability increases from the outset. The rate of disability progression varies between individuals. For some, disability may progress very gradually, and may remain stable or even improve very slightly over a short period. For others the progression is more rapid and unrelenting. Although the degree of disability will vary, the uncertainty of prognosis is universal. From the early stages of PPMS, quality of life is markedly affected and deteriorates as the disease progresses. People with PPMS are diagnosed later in life leading to complications with co-	Thank you for your comment. The economic model provided by the company reflects people with primary progressive multiple sclerosis rather than a relapsing form of the condition. This included using data from people with primary progressive multiple sclerosis obtained from a registry to model the condition. The committee have acknowledged that data on utility values for EDSS state from the ORATORIO trial (which only enrolled people with primary progressive multiple sclerosis) are appropriate to use in the model. Section 3.15 of the FAD has been updated to reflect this. Where data for EDSS states were not available from the trial, utility values obtained from people with primary progressive multiple sclerosis from Orme et al. were used (as described in the company's original submission).

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			morbidities. As a result, MS symptoms are more persistent and difficult to manage[5]. A clear consequence of this is a higher mortality rate for PPMS compared to relapsing MS. A recent Norwegian study found that life expectancy for relapsing MS was longer (77.8 years) than for those with PPMS (71.4 years)[6].	
22	Consultee	Multiple Sclerosis Trust	**Maintaining independence – upper limb function** We are pleased to see that the ACD acknowledges the importance of preserving upper limb function ULF) to allow people to continue working, engage in everyday activities and self-care (3.2, page 5). In our submission to the appraisal, we included quotes from people, all provided unprompted, which illustrate the value people place on hand and arm function: • *if I could preserve my hand function it would mean I could remain mainly independent which would benefit everyone.* • *Although I have limited mobility it is my hands deteriorating that I would like to slow or stop* • *I don't like being with people I don't know. I'm embarrassed because I can't use my hands properly so I have to have food cut up for me and I can't hold a glass or cup properly.* • *I have difficulty preparing meals as I am naturally right handed and I no longer have any strength in my right hand or arm. Also very little strength in my right leg and foot as I have foot drop on that foot. Dressing is also a problem.* Impairment of upper limb function has been completely overlooked in relapsing remitting MS trials, but is a very significant aspect of progressive MS disability. There is a growing recognition of the importance of ULF for many activities of daily living and maintaining independence. EDSS has been criticised for focusing too much on walking ability from 4.0 upwards and does not reflect changes in ULF. In ORATORIO, the nine hole peg test (9HPT), the gold standard for assessing upper limb function[7], was measured throughout the study. A 20% increase in the time taken to complete the 9HPT was used as one of the measures of disability	Thank you for your comment. The committee noted the importance of preserving upper limb function for people with multiple sclerosis (see section 3.2 of the FAD) and considered evidence submitted by the company relating to upper limb function from the ORATORIO trial and an open-label extension of the trial. The committee concluded that it is not appropriate to include additional utility decrements for upper limb dysfunction in the economic model. This was because upper limb function was an exploratory endpoint in the ORATORIO trial and the committee questioned why the company had selected this outcome to include in the model rather than the many other exploratory endpoints measured. The committee also heard from the ERG that the measure of upper limb function used in ORATORIO (changes in time to complete the 9-hole peg test) may not reflect changes in upper limb function that matter to people, such as reduced ability to wash, dress and feed themselves. It further considered that including decrements for upper limb function, decreasing utilities as people progressed through EDSS states, and carer disutilities likely overestimated the effect of ocrelizumab on slowing disability progression. Section 3.16 of the FAD has been amended to reflect this. In addition, the committee concluded that ocrelizumab was not cost effective for treating primary progressive multiple sclerosis at the patient access scheme price even in the company's base case analysis - which included additional utility decrements for upper limb dysfunction (see section 3.17 of the FAD).

[5] Holland NJ, et al. Meeting the needs of people with primary progressive multiple sclerosis, their families and the heal-care community. Int J Ms Care 2011;13:65-74
[6] Lunde HBM, et al. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psych 2017;88:621-25
[7] Feys P, et al. The nine-hole peg test as a manual dexterity performance measure for multiple sclerosis. Multiple Sclerosis 2017;23:711-20.

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			progression, a measure which is widely regarded as a clinically meaningful worsening[8]. Ocrelizumab reduced the time to 24-week confirmed progression on 9HPT by 45% for both hands, 35% for stronger hand and 40% for weaker hand, compared to placebo. The ACD criticises the manufacturer (3.21, page 17) for applying a utility decrement to each EDSS state for people with upper limb dysfunction. We believe this is appropriate as EDSS does not discriminate between changes in ULF. Maintaining ULF and therefore independence for longer clearly represents significant cost savings for the NHS, social care and reduces informal carer burden.	
23	Consultee	Multiple Sclerosis Trust	**Maintaining independence – mobility** A recent analysis of ORATORIO data has found that ocrelizumab treatment was estimated to delay the need for a wheelchair by 7 years compared to placebo; the median time-to-wheelchair was an estimated 19.2 years for ocrelizumab-treated patients and 12.1 years for the placebo group[9]. Maintaining mobility and therefore independence for longer clearly represents significant cost savings for the NHS, social care and reduces informal carer burden.	Thank you for your comment. The effect of ocrelizumab on slowing disability progression (through the EDSS stages) was included in the company's economic model. The committee noted that slowing disability progression will allow people with multiple sclerosis to continue working, engage in everyday activities and care for themselves for longer, and considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness.
24	Consultee	Multiple Sclerosis Trust	**Best supportive care** The ACD states that cost-effectiveness estimates for ocrelizumab compared with best supportive care alone are too high (section 1, page 3). Best supportive care is not defined in the ACD, nor are costs provided, so it is impossible for us to comment on the composition and level of NHS services that is assumed to be available across England and Wales. There is currently no research or professional consensus on what best supportive care for PPMS might be or how much it might cost. The concept of best supportive care is idealistic. It is unrealistic to assume that all people with MS have access to high quality care that fully meets their needs. The reality is that people with MS often have very limited access to services.	Thank you for your comment. Best supportive care in the economic model is described in the company's submission (which is available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10153/documents). For example, details on costs and resource use can be found in section B.3.5.2. To model the progression of disability between EDSS states in the absence of ocrelizumab in its economic model, the company used data from people with primary progressive multiple sclerosis from a registry (as described in the company's submission and in section 3.11 of the FAD). At consultation, the company

[8] Kragt JJ, et al. Clinical impact of 20% worsening on timed 25-foot walk and 9-hole peg test in multiple sclerosis. Multiple Sclerosis 2006;12:594-98.
[9] Butzkeuven H, et al. EPR1087 Risk of becoming wheelchair-confined in patients with primary progressive multiple sclerosis: data from the ORATORIO trial and a long-term real-world cohort from MSBase Registry. Eur J Neurol 2018;25(Suppl 2):320.

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			It is clear from the data collected in our survey that people with PPMS have a high level of need for NHS care. Given the wide range of symptoms that people with PPMS may experience, it is important that there is access to a range of therapies delivered by skilled health professionals, competent in MS care. In reality, access to NHS and social care interventions such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. Calculation of the cost of providing best supportive care cannot assume an ideal situation where these services are readily available. We are aware that in some areas, people with PPMS have been effectively 'discharged' from MS services, either due to a perception that there is no treatment available for PPMS or due to limitation in service capacity. Overwhelmingly, the message that people receive from MS health professionals is that there is no treatment available for PPMS. The quality of and access to care is highly dependent on where an individual lives. An MS Society report found that 40 per cent of MS specialist centres failed to offer people with MS a truly multi-disciplinary clinic[10]. This was also reflected in the Royal College of Physicians national audit of services for people with MS which found only 43% of people said they knew they had access to specialist neuro rehabilitation and 57% said that they had access to specialist MS physiotherapists[11]. In 2011 the National Audit Office report for services for people with neurological conditions found that the case loads of MS nurses varied extensively in each Strategic Health Authority[12]. A more recent survey[13] conducted by the MS Trust in 2016 found that on average, people with progressive MS are seeing MS specialists much less often than people with relapsing MS. People with PPMS and their families go to great lengths to remain active and independent and do whatever they can to stay in work. This often involves paying privately for treatments with limited availability through the NHS, such as physiotherapy or chiropody, or treatments which are not available at all, such as Sativex and Fampyra. This further demonstrates that, on the ground, "best supportive care" does not meet the needs of people with PPMS. We do not believe that modelling accurately reflects the true experience of NHS	commented that 80% of the registry dataset it used came from Canada, Spain, Italy, the Netherlands and Australia. In addition, the company stated that these countries' healthcare systems are similar to the UK and are expected to adhere to similar definitions of primary progressive multiple sclerosis diagnosis and treatment. The company explained that they did therefore not expect this cohort to differ significantly from people with primary progressive multiple sclerosis in the UK. In addition, data from the UK MS Survey was used as the source of costs for people in EDSS states in the company's revised base-case economic model. In its revised base-case economic model the ERG also included additional costs for direct non-medical care (i.e. social care). The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis. So, unlike for relapsing–remitting multiple sclerosis, clinicians can only offer interventions designed to manage symptoms (see section 3.2 of the FAD). The committee concluded that ocrelizumab is a 'step change' in treatment for primary progressive multiple sclerosis, but that it had not been presented with evidence of any additional benefits not captured in the QALY measurements (see section 3.18 of the FAD).

[10] MS Society, MS 2015 Vision, (2011)
[11] RCP and MS Trust, National Audit of services for people with Multiple (2011)
[12] National Audit Office. Services for people with neurological conditions (HC 1586). TSO, 2011
[13] MS Trust. Is MS care fair? MS Trust; 2016

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			treatment for many people with PPMS and that, for some people, progression is more rapid due to limited availability of care.	
25	Consultee	Multiple Sclerosis Trust	**Treatment waning** There is no clinical evidence for treatment waning. The manufacturer has been very clear that ocrelizumab causes negligible levels of neutralizing antibody and has reported a sustained treatment effect in an open-label extension of a relapsing-remitting MS trial. While we acknowledge that it is difficult to extrapolate from two year clinical trial data to long term treatment, we wish to emphasise that there is no clinical evidence to support loss of efficacy. The ACD states (3.11, p11) "The ERG included treatment waning in its base case, implementing it by reducing the treatment effect of ocrelizumab on slowing disease progression between EDSS states by 50% after 5 years. The committee concluded that "the company's assumption of no waning of treatment effect was too optimistic, but the ERG's approach may be too pessimistic. The true waning of treatment is likely to lie between these 2 approaches." This highlights the arbitrary nature of assuming treatment waning. The use of treatment waning in multiple sclerosis technology appraisals has become de facto, in the absence of clinical evidence or biological plausibility, the only purpose being to force an increase in the ICER. Further research is clearly needed to ensure an evidence-based approach to treatment waning.	Thank you for your comment. The committee considered the data from the open-label extension study submitted by the company at consultation, which provided almost 6.5 years of data. However no data were provided to show a lack of treatment waning beyond this time. The committee concluded that the company's original assumption of no waning of treatment effect was too optimistic, and noted that in its revised base-case analysis submitted at consultation the company had assumed a treatment waning effect from 10 years. The ERG commented that data from the open-label extension were reasonable evidence to support the absence of a treatment waning effect beyond 5 years (as it had assumed in its original base-case) and in its revised base-case analysis had assumed treatment waning from 7 years. The committee concluded that, acknowledging the issues of open-label extensions (see section 3.8 of the FAD), the ERG's approach may still be too pessimistic. It concluded that the true waning of treatment effect is likely to lie between the company's and ERG's updated approaches, and that exploring assumptions of treatment waning between 7 years and 10 years is reasonable. Section 3.12 of the FAD has been updated to reflect this.
26	Consultee	Multiple Sclerosis Trust	**Conclusion** The MS Trust wishes to state in the strongest possible terms the potential benefits of ocrelizumab for PPMS in terms of meeting the huge unmet need, delaying disease progression, and the impact on the daily lives of this group of people. Although people do all that they can to minimise the impact PPMS has on their lives, they are all too aware that there is nothing that will slow down the progression of their disease. As well as the long-term impact on mobility, work and independence, the psychological impact of a future with PPMS should not be underestimated. Our research has highlighted that the message people received from MS health professionals is that there is no treatment available for PPMS, which adds to that burden. The introduction of disease modifying drugs for relapsing remitting MS has been the catalyst for significant improvements in MS services for people with relapsing	Thank you for your comment. The committee considered the impact on loss of confidence and depression that living with the condition causes, and the anxiety caused by learning that there are no treatment options to slow the disease process (see section 3.1 of the FAD). It also noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with primary progressive multiple sclerosis. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.

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			MS. The introduction of a treatment for PPMS would similarly result in a greater focus on services for progressive MS and a more pro-active approach to managing PPMS which would ultimately benefit a much wider group of people with PPMS than just those who might be eligible for ocrelizumab. We are delighted that NICE recognises the innovative nature of ocrelizumab and urge NICE, NHS England, the Department of Health and the manufacturer to find a solution which enables those eligible to access this drug as soon as possible.	NICE are open to engaging with the company and NHS England. However, as clarified during the committee meeting the committee can only consider prices agreed with NHS England (see section 4.6 of the TA process guide). NHS England confirmed to NICE that it cannot consider the commercial arrangement proposed by the company. So at its second meeting, the committee could only consider ocrelizumab at the price for the patient access scheme for relapsing remitting multiple sclerosis. Further, the committee heard from NHS England that they can only consider the type of arrangement proposed by the company in limited, specified circumstances, which do not apply to this case.
27	Patient expert	Mrs Yvonne Pettigrew	The market authorisation indication, considered by the ERG to be 'vague and subjective' has in my opinion created an avoidable lack of clarity in the understanding of "early primary progressive multiple sclerosis" in this context by defining this "in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity". Could consideration be given to changing this to "in terms of disease progression and level of disability" to be consistent with the ORATORIO trial? These two elements would enable: objective targeting of the eligible patient population; better definition of the start point; exclusion of the additional MRI costs.	Thank you for your comment. The marketing authorisation indication referred to is set by the European Medicines Agency (EMA). NICE can only appraise technologies within their marketing authorisation.
28	Patient expert	Mrs Yvonne Pettigrew	It is correct, as stated, that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis (PPMS). However it is incorrect that "clinicians can only offer interventions designed to control symptoms", rather they "can only offer interventions to potentially manage symptoms" as without disease modification they cannot be controlled and will continue to progress. It is this aspect of the disease that is most terrifying for patients.	Thank you for your comment. Section 3.1 of the FAD has been amended to specify that clinicians can only offer interventions designed to manage symptoms.
29	Patient expert	Mrs Yvonne Pettigrew	Defining who will benefit from ocrelizumab may not need to increase demand for MRI scans. By its very nature PPMS features symptomatic deterioration and functional decline which evidences the ongoing inflammatory activity. The 2013 revised McDonald criteria incorporated categorisation of active or not (based on recent clinical relapse or MRI lesion activity) and progressive or not (based on clinical assessment of disability) according the disease course in a preceding time period e.g. 1 year.	Thank you for your comment. The marketing authorisation for ocrelizumab specifies primary progressive multiple sclerosis "…with imaging features characteristic of inflammatory activity". NICE can only appraise technologies within their marketing authorisation. Identifying people with primary progressive multiple sclerosis who would be eligible for treatment with ocrelizumab would require MRI scans.

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			Would it therefore be reasonable to adopt the same criteria i.e. using clinical & functional systems assessment and the EDSS 3.0 - 6.5 as per the ORATORIO trial criteria to determine eligibility. (The former is necessary because at the lower / earlier grades of the EDSS, deterioration within sections may not effect a change in the score).	
30	Patient expert	Mrs Yvonne Pettigrew	The committee discussed the difficulties in defining "early" disease in NHS practice and concluded the EMA definition used for the marketing authorisation to be used. However, this brings with it the dependency on, and costs of, MRI scans. Would it be possible to review this decision and instead define 'early PPMS' in terms of confirmation of the early phase of deterioration using the "level of disability", 3.0 - 6.5 (to be consistent with the ORATORIO trial), and the confirmation of "disease progression" deterioration within previous time period e.g. 1 year (to be consistent with McDonald criteria)	Thank you for your comment. The definition of 'early' primary progressive multiple sclerosis used in the ORATORIO trial (used by the EMA) refers to EDSS score and time since onset of symptoms. The requirement for MRI scans relates to the requirement set out in the marketing authorisation that primary progressive multiple sclerosis should have "…with imaging features characteristic of inflammatory activity". NICE can only appraise technologies within their marketing authorisation. The committee concluded that defining 'early' disease in NHS practice is difficult but that, for the purpose of this appraisal, early primary progressive multiple sclerosis is as defined by the EMA for the marketing authorisation (as described in section 3.5 of the FAD).
31	Patient expert	Mrs Yvonne Pettigrew	Concerns raised about using data from the MSBase registry are understood. Can the committee make recommendation for a PPMS population long term follow-up registry to overcome this for future. Has the MS Register been considered ? 17048 people have joined the study so far with 29 participating MS Clinics. The EDSS is one of the 9 measures used.	Thank you for your comment. At the second committee meeting, the committee acknowledged that it was appropriate to use the MSBase registry to inform baseline transitions between EDSS states in the absence of treatment in the company's model. Section 3.11 of the FAD has been amended to reflect this. The choice of registry used in the model was made by the company. Further detail can be found in the company's submission (which is available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10153/documents).
32	Patient expert	Mrs Yvonne Pettigrew	"What would an acceptable stopping rule be?" I suggest "when there has been no evidence of disease progression i.e. assessed symptom deterioration and /or EDSS score increase, during a preceding 12 month time period.	Thank you for your comment. The committee considered what an appropriate stopping rule for treatment would be at the second committee meeting, including your response to the question on this asked at consultation. The committee's discussion focussed on whether treatment should be stopped when a person has progressed to EDSS 7.0 (as for relapsing remitting multiple sclerosis) or 8.0; rather than when people were not progressing. The committee concluded that, although there is considerable uncertainty about an appropriate stopping rule, it had not been presented with any evidence to support a stopping rule that differed by type of multiple sclerosis (see section 3.14

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				of the FAD).
33	Patient expert	Mrs Yvonne Pettigrew	Given that data from the ongoing trial is unlikely to address the uncertainties identified by the committee, specifically related to 'the extent of treatment waning and how long people would stay on treatment' I suggest it is essential the company to build this into future studies. In the interim is there a subset of the ORATORIO trial who continued to show disease progression that could illuminate understanding of when to stop treatment and the effect this may have on affordability?	Thank you for your comment.
34	Patient expert	Mrs Yvonne Pettigrew	Very disappointed that cost benefit cannot be demonstrated as ocrelizumab represents such a life-changing step change for patients with PPMS. Question: If 'early PPMS' could be more easily defined by "early phase of disability (EDSS 3.0 - 6.5) and active progression of symptoms within recent 12 month", and the end point of treatment be clarified as "when there has been evidence of further progression (using EDSS) whilst on treatment", could the MRI costs be excluded, and the time on treatment more accurately costed to potentially deliver an affordable model ?	Thank you for your comment. NICE can only appraise technologies within their marketing authorisation. Therefore the definition of early primary progressive multiple sclerosis used by the EMA and the need for the condition to have imaging features characteristic of inflammatory activity (requiring MRI scans) needs to be considered in assessment of cost effectiveness. In addition, the committee concluded that although there is considerable uncertainty about an appropriate stopping rule, it had not been presented with any evidence to support a stopping rule that differed by type of multiple sclerosis (see section 3.14 of the FAD), noting that people stop disease-modifying treatments in relapsing–remitting multiple sclerosis when a patient has an EDSS stage 7.0 for more than 6 months. The committee also noted that there were no scenarios presented in either the company's original or revised analyses in which ocrelizumab was cost effective, and concluded that ocrelizumab is not cost effective for treating primary progressive multiple sclerosis at the current patient access scheme price.
35	Public	Patient 1	Ocrelizumab is thought now to possibly delay progression to wheelchair by up to 7 years in PPMS patients - this news from the 4th Congress of European Academy of Neurology following phase 3 trials after 24 months of data. Does NICE not recognize that no other treatment has been effective in PPMS except Ocrevus? And now to deny something that can have a very meaningful impact for 7 years in people with PPMS...shame on you. I don't have PPMS, I have RRMS, but this announcement made me cry for it shows the lack of care for the quality of life of people with chronic progressive diseases in this country. Also this seems economically shortsighted as the economic production from people with PPMS in the economy by working much longer could be alleviated. If someone can work 7	Thank you for your comment. The effect of ocrelizumab on slowing disability progression (through the EDSS stages) was included in the company's economic model, and therefore cost-effectiveness estimates, using a measure of treatment effect on confirmed disability progression (CDP) confirmed after 12 or 24 weeks. The committee noted the unmet need for disease-modifying treatments for this condition, and the

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			years longer, this should be taken into account into so-called "cost-benefit" analyses. https://multiplesclerosisnewstoday.com/2018/06/15/latest-ocrevus-data-in-ppms-at-ean-2018-meeting-announced-new-trials/	substantial effect that it has on the lives of people with the condition and their families. The committee also noted that slowing disability progression would allow people to continue working, engage in everyday activities and care for themselves for longer (see sections 3.1 and 3.2 in the FAD for further details of committee considerations). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness in its decision-making.
36	Public	Carer 1	You are discriminating against a whole group of PPMS people compared to RRMS because there is NO treatment (drug) available on the NHS to make a cost comparison to what a person with PPMS receives, ie, Â£0.00. My husband's sole treatment at the moment is a yearly appointment with his consultant and a physiotherapist. That's it! NICE can prevent his deterioration which WILL result in my husband being incapacitated. You have just destroyed the hopes of a whole group of sufferers, please reconsider your decision, if you prevent him now from deteriorating further, it will be a long term saving for the NHS and its future.	Thank you for your comment. Because no disease-modifying treatment for primary progressive multiple sclerosis is available, the cost effectiveness estimates were made by comparing treatment with ocrelizumab to best supportive care (that is, no disease-modifying treatment used). The committee considered the unmet need for disease-modifying treatments for this condition, the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
37	Public	Patient 2	This is the first ray of hope for us with PPMS. DMD are not working for me (diagnosed 2 years ago) so would urge you reconsider this.	Thank you for your comment. The committee considered the unmet need for disease-modifying treatments for this condition, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
38	Public	Patient 3	Ocrelizumab has been rejected for PPMS sufferers. They say that we should just carry on with our current PPMS drugs. I am not aware of any other drugs for PPMS, so how can we carry on with it? Ocrelizumab was our first and only chance!	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis,

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				and considered the unmet need for disease-modifying treatments for this condition (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
39	Public	Patient 4	I am newly diagnosed with ppms and im scared my walking has already started to deteriorate please reconsider allowing ocrevus so I can have a small quality of life as opposed to none. Please please reconsider your decision	Thank you for your comment. The committee noted the unmet need for disease-modifying treatments for this condition, and the substantial effect that is has on the lives of people with the condition and their families. The committee also noted that slowing disability progression and preserving upper limb function would allow people to continue working, engage in everyday activities and care for themselves for longer (see sections 3.1 and 3.2 in the FAD for further details of committee considerations). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
40	Public	Patient 5	I was diagnosed with Primary progressive MS in 2010 and my condition is gradually worsening as time goes by. Ocrelizumab has been approved by NICE for use on the NHS for relapsing remitting multiple sclerosis whereas there are lots of available treatments for this type of MS at the moment. Clinical trial results show that ocrelizumab slows disability progression in Primary progressive as well as relapsing remitting MS. Ocrelizumab is the ONE AND ONLY option for a slower disability progression for people in the Primary progressive MS population. The slower disability progression is the reason that ocrelizumab has been approved for relapsing remitting MS so why cannot it be approved for Primary progressive MS. I believe that people with Primary progressive MS in general are being discriminated against by not having Ocrelizumab made available to them on the NHS, because it is the only approved disease-modifying treatment for use in Primary progressive multiple sclerosis.	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis, and considered the unmet need for disease-modifying treatments for this condition (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and

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				primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
41	Public	Patient 6	As a recently diagnosed sufferer of PPMS I am very disappointed at this decision from NICE. With no NHS drugs, treatment or support offered except the services of a consultant and an MS nurse once a year it would be good to have the opportunity to take a drug which has been proven to delay progress of the disease. I understand the drug is expensive but it may well delay the time when I need various aids around the house and a wheelchair, all of which cost the NHS. At the moment I am funding my own physiotherapy because there is none available in my area on the NHS. I may well not always be able to afford this.	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-modifying treatments approved for the condition. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
42	Public	Patient 7	So very disappointed with outcome of ocrelizumab for rejection for ppms,lived with this for past 8 years with no hope, this was my only hope So disappointed on rejection of ocreizumab for ppms. it was my only hope	Thank you for your comment. The committee considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
43	Public	Carer 2	Please please re-consider Ocrelizumab for Primary Progressive patients as my partner suffers from this awful illness for which there is no treatment. He has tried steriods and other medications to no avail. We were waiting with bated breath for this drug to be released, to halt his progression, and are devastated to find it is not being allowed. I have followed Ocrelizumab User Groups on web-sites on FB and they have had great results in America and Europe. Even if we could pay some money towards getting it, if you would only release it. Relapsing Remitting patients have many other drugs to use and experience relapses, while my partner suffers every day and worsens every day. Please re-consider releasing this drug to a group of people who have nothing to live for. Many thanks.	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-modifying treatments approved for the condition. The committee further considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition

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				alongside the evidence on clinical and cost-effectiveness when making its decision.
44	Public	Patient 8	I feel very disappointed in this decision. There are no other treatment options for me as a sufferer of ppms. The only treatment I have ever been offered is alleviation of symptoms in the hope that something will come along to help in the future. Ocrevus was a potential "help in the future". Without this, all I face is a worsening of my condition being "managed".	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-modifying treatments approved for the condition. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
45	Public	Patient 9	My name is [redacted] and I am 59 years of age. I live in [redacted] and work as a professional engineer in [redacted]. In 2006, I was diagnosed with Primary Progressive Multiple Sclerosis (MS) which came as a major blow. Over the years, I have witnessed my walking steadily worsen. As a result, I now walk with a single stick. At night, I experience strong spasms which interrupt my sleep and interfere with my quality of life. When out and about, I have to be extremely careful to not trip and fall over which has happened a number of times over the years. My reduced mobility limits what I can do on a daily basis; trips out have to be planned for like a military campaign. I worry about the future and what that will bring for me. It's hard for my wife [redacted] who supports me as much as possible, says nothing but I know that she worries too. When Ocrevus (Ocrelizumab) was initially announced by Roche in 2015 as a major game changer for MS, and in particular Primary Progressive MS, it filled me with huge and excitement and hope for the future. I have tracked it's progress with great interest. I was so pleased to read that it has been recently approved by NICE for use by the NHS for Relapsing Remitting MS; I believed it was only a formality that it would be approved for Primary Progressive MS within the next few months. I was totally devastated to learn from an MS Trust newsletter in the last few days that NICE have rejected it's use for Primary Progressive MS by the NHS. This piece of news completely extinguished my single source of hope for the future in altering the course of deterioration caused by this awful condition. I would like to appeal to NICE to please reconsider their decision for my sake and the thousands of others in the UK affected by Primary Progressive MS.	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-modifying treatments approved for the condition. The committee also considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
46	Public	Patient 10	Ocrelizumab please help us patients with PPMS there are no medications out there for us at all. Our consultants have been telling us great things about this drug. Just give us the opportunity to try. RRMS have so many choices give us a break!	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-

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				modifying treatments approved for the condition. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
47	Public	Carer 3	See emailed comments to [redacted] MP. Dear [redacted] You helped us in our fight to get [redacted]'s PIP reinstated. The following points highlight a continued lack of help and support from our healthcare system. 1. We were forced in to a prolonged and degrading battle with the DWP and Capita to get [redacted]'s PIP reinstated. 2. There is no longer a specialist MS consultant at Leicester General hospital, [redacted]'s last two appointments have both been cancelled and she has not seen an MS specialist in over a year with no prospect of seeing one at all in 2018. 3. NICE have decided not to approve Ocrelizumab for use on the NHS despite it being the first and only disease modifying drug currently available anywhere in the world for the treatment of primary progressive Multiple sclerosis - PPMS. NICE acknowledge the effectiveness of Ocrelizumab in slowing down the disease but say it does not represent value for money compared to other routine PPMS treatments available on the NHS, these so called treatments only treat the symptoms not the cause, in [redacted]'s case anti depressants, anti spasm and neural pain control drugs that have little to no effect and do not slow the progression of her disability which is not cost effective when you consider she is likely to be more of a burden on the NHS sooner and longer without the benefits of Ocrelizumab. NICE have approved it for the treatment of relapsing MS but this makes no sense, it would have been more plausible to approve it for PPMS only on the grounds of cost and the numerous disease modifying drugs already available on the NHS for the relapsing type. Our hopes and the hopes of many other PPMS sufferers were pinned on this new drug, we now have no hope. We contribute our hard earned tax pounds to the state but when we need help we are forced to beg for it, this is a sad and shameful indictment of the country we live in. I would be grateful for any assistance you can once again provide in highlighting these issues to your government colleagues in Parliament.	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis, and considered the unmet need for disease-modifying treatments for this condition (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE's recommendation on the use of ocrelizumab for treating relapsing-remitting multiple sclerosis had no impact on the committee's decision about whether ocrelizumab should be recommended for primary progressive multiple sclerosis; which was based on the clinical- and cost-effectiveness of the treatment in this population. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.

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			I will be taking our plight back to the press.	
48	Public	Patient 11	In your Initial response for use with PPMS you mention "routine treatments", what do you mean asI was told my neurologist that nothing was yet available.	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis, and considered the unmet need for disease-modifying treatments for this condition (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
49	Public	Patient 12	I'm an italian patient with Primary Progressive Sclerosis. For us multiple sclerosis advances quickly and ocrelizumab can help us to feel a little better. Ocrelizumab is available on WEB but the cost, over 8.000 USD each, (3 infusions are needed in 6 months, so are over 24.000 USD), is not suistanable for those who are no rich. Please, please, please, do not cancel the hope for a less dark future. British are a great people and the gratness is measured by the support of those in need of help.	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-modifying treatments approved for the condition. The committee also considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
50	Public	Patient 13	Approval should be given for use of ocrelizumab for PPMS if recommended by the attending consultant. Manufacturer funded trials should be permitted. Cost savings to the NHS need to be emphasised as any improvement in PPMS suffers health will be less draining on the NHS The drug should be available to all MS sufferers for whom the drug was intended for,	Thank you for your comment. The cost-effectiveness estimates for ocrelizumab for primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company, using the approved commercial arrangement price. Because of this, ocrelizumab was not recommended for treating early primary progressive multiple sclerosis. The committee considered the data that would be generated by an upcoming phase IIIB trial the company will carry out, but concluded that data from the trial is unlikely to address the uncertainties identified by the committee, such that ocrelizumab could then be considered cost effective (see section 3.19 of the ACD).
51	Public	Patient 14	I have been diagnosed with secondary progressive multiple sclerosis in	Thank you for your comment. This appraisal applies to

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			march,2017.I had to take early retirement at the age of 58 because I couldn't work anymore. There is no treatment for me out there and I saw my consultant 2 weeks ago and gave me some hope when he talked about this new drug and that he said he hoped that it would be suitable for me. But with Nice saying no to this drug all hope has now gone that it might be suitable for me with secondary progressive multiple sclerosis.I am getting worse each year and you have just dashed all my hopes.	ocrelizumab for primary progressive multiple sclerosis only. Secondary progressive multiple sclerosis was outside of the scope of this appraisal.
52	Public	Patient 15	I would like NICE to reconsider their recent decision regarding Ocrelizumab for sufferers of PPMS. Since my diagnosis in 2015 I have felt totally isolated with nothing on the horizon in terms of medication for this dreadful condition. I've spent most of my working life helping others and have never asked for anything in return. The approval of Ocrelizumab would at the very least have given me and MANY others a glimmer of hope in an otherwise dark abyss. I would respectfully ask you to reconsider your decision thus giving many of us something positive to look forward to as we have precious little thus far. Kind regards	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-modifying treatments approved for the condition. The committee also considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
53	Public	Patient 16	Hello, As a PPMS sufferer I am deeply, deeply saddened to hear the initial result regarding Ocrevus. It is unfair to be have been diagnosed with MS in the first instance as a 42 year old, previously very active mum of two. To then be told there are no possible drugs available to potentially help with my condition was heartbreaking. The only glimmer of hope on the horizon was the potential availability of Ocrevus. It is very hard to cope on a day to day basis and having to explain the situation to my two boys was indescribably difficult. To then have my only chance of improvement taken away because of what type of MS I have? Ludicrously unfair. I feel discriminated against through absolutely no fault of my own. I anxiously wait further comment on this consultation.	Thank you for your comment. The committee noted that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families and that there are currently no disease-modifying treatments approved for the condition. The committee also considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple

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				sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
54	Public	Patient 17	I am extremely saddened to hear this news today. I am 38 years old, and I have SPMS. I was diagnosed with RRMS, in 2009, and went onto Rebif for a few years, and then Fingolimod, until 2017. I try to be proactive, and try to stay positive for the future, but with there being no medication for SPMS, this is incredibly challenging. As is life in general when living with this disease. News of Ocrevus being made available gave me some hope for the future. Now once again, my hopes have been crushed, and future life uncertain. I urge you to please overturn your decision, and give MS sufferers some hope!!!	Thank you for your comment. This appraisal applies to ocrelizumab for primary progressive multiple sclerosis only. Secondary progressive multiple sclerosis was outside of the scope of this appraisal.
55	Public	Carer 4	Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both upsetting and extremely concerning.	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited

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				NHS resources in all scenarios presented by the company using the approved commercial arrangement.
56	Public	Public 1	'Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both upsetting and extremely concerning.'	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
57	Public	Public 2	Ocrevus is the ONLY approved, effective treatment in the world for PPMS. In not approving it for this condition it discriminates against and actively disadvantages sufferers of PPMS solely on the grounds of the type of condition they have. It is puzzling that others suffering from a different variant of MS have had the treatment approved. Why are people with PPMS being treated less fairly than those with RRMS? The decision of NICE is both upsetting and extremely concerning.	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement..

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58	Public	Public 3	Why are people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both confusing and extremely upsetting to those entire families having to live with this debilitating affliction.	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
59	Public	Public 4	Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both upsetting and extremely concerning!	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
60	Public	Public 5	Ocrevus is, I believe, the only approved, effective treatment in the world for PPMS.	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and

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			To not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Grateful if you would explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both very upsetting and extremely concerning.	relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
61	Public	Public 6	'Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both upsetting and extremely concerning.'	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
62	Public	Public 7	Two close members of my family had and have PPMS. During my professional career I came in contact with many others. I observed with dismay and sadness the detrimental effects this has on the lives of these sufferers. It is unjustifiable and inhumane to deprive PPMS patients of Ocrelizumab on any grounds whatsoever	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis, and considered the unmet need for disease-modifying

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			this being the only approved, effective treatment in the world for those with this diagnoses. To exempt the PPMS patients from the benefits while at the same time allowing the the treatment for RRMS patients is discriminatory and unacceptable. This is simply unequivocal. How many more sufferers need to experience these or similar events in order to attempt to save expense within the NHS? If it is the object of NICE to serve the benefit and protect NHS patients, surely it is also to provide the proven drugs and the methods available to facilitate this.	treatments for this condition (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
63	Public	Public 8	It seems to me that failure to provide this treatment discriminates against PPMS sufferers as approved treatments are available for RRMS.	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-

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				effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
64	Public	Public 9	It's appalling that even though this has such substantial benefits to those effected the government is proving to be the obstacle in providing this life saving remedy	Thank you for your comment.
65	Public	Public 10	This is a very disappointing decision and one that I hope will be reversed at a later date. There are currently no treatments of this kind available for PPMS and people suffering should be given access to Ocrelizumab to improve their quality of life.	Thank you for your comment. The committee noted that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis, and considered the unmet need for disease-modifying treatments for this condition (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
66	Public	Patient 18	Hi, I have been diagnosed for the last ten years with PPMS. Things have changed and developed over the years and I now use an FES to help me walk. Other than that I take no medication for my condition. I had heard about the news of a new drug; Ocrelizumab that was going to help people like me with PPMS by halting the development of MS. I hear that it's going to be rejected now for people with the same condition as me but will now be used for RRMS patients. This really worries and upsets me as there is so very little out there to help me and I just feel like we've been hung out to dry, while the RRMS people have no end of treatments and medications at their disposal. I know both versions of MS are horrible but I feel like as the MS takes a stronger hold I'm running out of time! I just hope you might be able to reverse the decision and make it available to me and others? Many thanks	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
67	Public	Public 11	The wife of a good friend suffers from this and I am told that Ocrevus is the proven, effective treatment in the world for PPM. Consequently, not to approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved.	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating

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			This does not seem fair to me.	relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
68	Public	Patient 19	I was diagnosed with Primary Progressive MS about 2 years ago. I was determined to deal with this positively and have moved to a bungalow and have continued to stay as healthy as possible by taking regular exercise and eating properly. However my symptoms are increasing. I was devastated to read that NICE have removed the possibility of slowing down the progression of this disease and that I am likely to become less independent and a burden on the state more quickly than necessary. I feel that MS is a poor relation compared with other conditions and I hope very much that NICE will reconsider its decision in order to give MS sufferers such as myself some hope of delaying the disease.	Thank you for your comment. The committee considered the unmet need for disease-modifying treatments for this condition, the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
69	Public	Public 12	'Ocrevus being THE ONLY proven, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? And how you can defend the reasoning in offering to one variant and not the other?	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating

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				primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
70	Public	Public 13	Why are you discriminating against those who suffer with PPMS when other types of condition such as RRMS receive their treatment? Quality of life and live itself are at serve risk because of this.	Thank you for your comment. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
71	Public	Patient 20	In no certain order : There is no treatment for PPMS, any drug that can have the potential to prevent/minimize further disability will be cheaper to the NHS/Govt as a whole than the costs to the country as a whole of increasing disability. The costs of numerous GP appointments, MS Nurses, hospital appts hospital admissions , including social care input from home carers to nursing care. The cost of people being unable to work & be retired due to ill-health, so cannot contribute to society but become a "financial burden" relying also on benefits. There is also the great personal impact not just for the person with PPMS but also the strain on family, friends and the community at large. People should be given the opportunity via their Neurologists to try the drug, if it shows no improvement for the individual then it can be stopped, but not to allow someone the opportunity to try it is cruel.	Thank you for your comment. The committee considered that many people with primary progressive multiple sclerosis eventually need support and care from family members or friends, and that the condition can substantially affect the lives of people with the condition and their families. Furthermore, slowing disability progression and preserving upper limb function allows people to continue working, engage in everyday activities and self-care for longer (see sections 3.1 and 3.2 of the FAD for more detail). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
72	Public	Patient 21	I have had Primary Progressive MS for past 20 years and have not received any medication to relieve my symptoms Ocrelizumab is the first drug that shows any promise of slowing down the	Thank you for your comment.

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			progression of the disease and I urge NICE to reconsider their decision.	
73	Public	Public 14	An extremely disappointing initial decision on this very promising treatment. Please reconsider the millions of people that are suffering as a result of MS.	Thank you for your comment.
74	Public	Patient 22	My sister (PPMS) and I (RRMS) were both diagnosed with MS in 2016 and 2017. Almost immediately I was prescribed my DMT of choice, Tecfidera. My sister was advised that, should Ocrevus be approved for UK use, she would be a strong candidate in terms of criteria. I am not medically trained and therefore not able to contribute in terms of technical details. However, I strongly object to the NICE decision to deny approval for a UK licence for patients with PPMS on the following grounds: 1.2 'Costs are much higher than those NICE normally considers an acceptable use of NHS resources' Given that the NHS is currently finding the cost of my prescription for Tecfidera as acceptable (approximately £17,000-£20,000 per annum) the figures cited on the consultation document for Ocrevus do not appear remarkably dissimilar and one would question why Ocrevus for RRMS patients is not objectionable to the NHS. There is nothing 'normal' about MS; the NICE response to the drug being ethically and medically acceptable cost-wise for RRMS patients and not PPMS patients is discriminatory on grounds of condition-type, for which the boundaries and definitions are case-by-case, often the subject of uncertainty. You allude to this in Section 3.3 of the consultation document. 3.3 Likely to increase demand for MRIs This would need to be clarified as to whether the objection is regarding the cost of MRIs to the UK on an annual basis, or whether there is an agreed and set limit per patient of entitlement to MRIs which, I do not believe there is. I have been able to obtain and MRI on request and was never made aware by the NHS that I would be resticted on future MRIs to monitor my treatment efficacy and condition. There are many factors inherent in the UKs ageing popiuation which may, or may not warrant an increase in demand for MRIs. This is to be anticipated within any country with an increasing age-expectancy. Again, it is discriminatory to suggest that PPMS patients are less-entitled to a possible increase in their MRIs and should therefore not be described an effective DMD. The reduction in the use of gadilinium over time due to concerns over long-term safety is a recommendation which extends beyond the confines of MS; therefore this is not a consideration which should be a factor in declining approval for Ocrevus. Risks are always associated with operations, procedures and medications; this is why patients sign consent forms.	Thank you for your comment. The ACD, and FAD, state that cost-effectiveness estimates for ocrelizumab compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement. Decisions on whether to recommend treatments are based on estimated cost-effectiveness rather than the absolute cost of the treatment. This is estimated based on the changes in all costs related to use of a new treatment and changes in QALYs (a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life) that are expected to be generated through use of the treatment. The committee noted that because the marketing authorisation limits treatment to early primary progressive multiple sclerosis with imaging features that are characteristic of inflammatory activity, and that repeated MRI scans are not currently done to monitor inflammatory activity because no disease-modifying treatments are available, the use of ocrelizumab could result in increased demand for MRI scans (see section 3.3 of the FAD).

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			3.11 The company assumed that [efficacy] did not waiver over time. As a non-specialist, I would argue that there is no guarantee for any DMD on its projected efficacy over time. If there were, there would be no degeneration or worsening of symptoms with any variant of this, and other conditions. And on that basis, the NHS continues to prescribe me Tecfidera at great cost to the NHS. To deny approval for funding Ocrevus to treat PPMS makes no medical or ethical sense, given the arguments against approval. This medication has shone the single light of hope on the horizon for patients with PPMS for the first time; to deny patients the right of access which Europe, the United States and Canada has provided its citizens makes no sense based on the objections raised by this document. It discriminates against patients based on the type or variant of the same disease when clarity of definition is often questionable. It assumes that the burden of cost for increased MRIs and Ocrevus prescription will be greater than the cost of longer-term care and other NHS resources, an assertion which is impossible to predict. NICE initially made similar objections to the prescription of Ocrevus for RRMS in 2018 which it has now overturned, given that Ocrevus has now been approved for UK use with RRMS patients. It is with my great hope and anticipation ,that NICE will make the same decision with Ocrevus for the treatment of UK patients with PPMS.	The extent of any treatment waning was considered because of its impact on the cost-effectiveness estimate for treatment. The committee concluded that the true waning of treatment effect is likely to lie between the company's and ERG's updated approaches, and that exploring assumptions of treatment waning between 7 years and 10 years is reasonable. Section 3,12 of the FAD has been amended to reflect this. The committee considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the

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				approved commercial arrangement.
75	Public	Public 15	I urge you to reconsider your decision on Ocrelizumab as a treatment for PPMS . There are currently no treatments available , this puts people with a diagnosis of PPMS at a distinct disadvantage . My husband was diagnosed in 2006 . I have watched his mobility decrease steadily in the intervening years . He can only walk short distances with a stick and requires the use of a wheelchair for longer distances. Trips out have to be planned meticulously in advance as he is unable to use public transport. He has remained positive despite a significant decline in his independence & a curtailment of his hobbies & interests (playing music, photography) He has been proactive in the management of his condition and is vigilant about doing his home exercise programme. He also swims up to 3 times a week . He subscribes to the MS trust newsletter & has remained optimistic that there will be a treatment available soon for PPMS . Please give hope to my husband, myself & all the other people with PPMS by reversing your decision on Ocrelizumab	Thank you for your comment. The committee considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition. Section 3.1 of the FAD has been updated to reflect this. It also noted the unmet need for disease-modifying treatments for this condition, and the substantial effect that is has on the lives of people with the condition and their families. The committee also noted that slowing disability progression would allow people to continue working, engage in everyday activities and care for themselves for longer (see sections 3.1 and 3.2 in the FAD for further details of committee considerations). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
76	Public	Patient 23	Given the limited range of treatments available for PPMS the argument of not offering value for money I find abhorrent. I really could not care what the treatment costs when non-vital cosmetic surgery and IVF is offered on the NHS. The issue surrounding approving a drug for use should be around risk to the patient which ultimately is up to the patient anyway. So approve the medication and leave the application of the medication up to the neurologist and the patient.	Thank you for your comment.
77	Public	Patient 24	I'm a suffer of PPMS. Ocrelizumab has been approved for treatment of RRMS. I believe the decision not to approve ocrelizumab for treatment PPMS is wrong for the following reasons. 1. Whilst there are multiple DMTs for RRMS, there are currently none licensed for PPMS. 2. There are fewer suffers of PPMS that RRMS. I understand that only 14% or so of MS suffers have PPMS. The cost for the NHS therefore would be significantly less than approving it for RRMS.	Thank you for your comment. The committee noted the unmet need for disease-modifying treatments for this condition, and the substantial effect that is has on the lives of people with the condition and their families (see sections 3.1 and 3.2 in the FAD for further details of committee considerations). It considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE's recommendation on the use of ocrelizumab for treating relapsing-remitting multiple sclerosis had no impact on the committee's decision about whether ocrelizumab should be recommended for primary

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				progressive multiple sclerosis; which was based on the clinical- and cost-effectiveness of the treatment in this population. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement..
78	Public	Patient 25	There are no other treatments available for PPMS.	Thank you for your comment. The committee noted the unmet need for disease-modifying treatments for this condition, and the substantial effect that is has on the lives of people with the condition and their families (see sections 3.1 and 3.2 in the FAD for further details of committee considerations). It considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
79	Public	Patient 26	I was diagnosed with PPMS in October 2014. My mobility and quality of life is deteriorating much faster than I had anticipated. I have had to finish work a job and people I loved. Tasks I can carry out are becoming fewer. Ocrelizumab gave me some hope. Maybe the progression of my disease could be slowed down. I spoke to my consultant who said I would be suitable and in fact ideal for treatment with Ocrelizumab. I waited for Ocrelizumab to get a European licence for RRMS and PPMS. I saw NICE reject and then approve Ocrelizumab for RRMS. I waited for the NICE decision on PPMS. This is the first disease modifying drug for PPMS and so I was confident it would be approved. To say I was disappointed when NICE rejected Ocrelizumab for treatment for PPMS is an understatement. My lifeline was gone. I hope that NICE will reconsider and approve Ocrelizumab for PPMS. I know there is a cost factor and NICE consider treatment not to represent value for money to the NHS but for me and others with PPMS this is the only treatment that will slow down the progression of the disease. The only routine NHS treatment is symptom management, prevention of complications and health and wellbeing. People with PPMS need a treatment that will slow down the progression of their disease. Ocrelizumab is that treatment. I hope NICE will reconsider and approve Ocrelizumab as an NHS treatment for early PPMS.	Thank you for your comment. The committee considered that many people with primary progressive multiple sclerosis eventually need support and care from family members or friends, and that the condition can substantially affect the lives of people with the condition and their families. Furthermore, slowing disability progression and preserving upper limb function allows people to continue working, engage in everyday activities and self-care for longer. It also considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition (see sections 3.1 and 3.2 of the FAD for more detail of committee considerations). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
80	Public	Carer 5	You've stated that there is no current treatment for Primary Progressive MS. My mother has this type of MS and it is heart breaking to see her deteriorating every day. This drug was a glimmer of hope for her. You've recognised that this drug can help with PPMS. A lot of people had hope resting on this drug being passed and it's soul crushing to see that it has been rejected because of cost. What is the cost of human life? There are treatments for other kinds of MS but not PPMS. Not	Thank you for your comment. The committee considered that many people with primary progressive multiple sclerosis eventually need support and care from family members or friends, and that the condition can substantially affect the lives of people with the condition and their families. It also considered the

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			everybody can afford to pay the extortionate fees that are associated if trying to get this drug privately. I really do hope that you reconsider your decision, without this drug I'm sure that my mother and many other people who are living with PPMS will continue to deteriorate.	impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition (see sections 3.1 and 3.2 of the FAD for more detail). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
81	Public	Patient 27	Yes have PPMS -I am dumbfounded that the decision has been made not to approve the first ever drug with a licence for PPMS-I have recently had to give up work due to my condition and that means I pay less tax and may have to claim benefits. This does not make financial sense to take people out of employment when you have the ability to improve their lives. To licence for RRMS when there is a huge amount of choice of treatment seems senseless. Of course, I understand the cost implications but I currently I have no treatment so any cost will compare badly to that of current (no!) treatment. Also, pharmaceutical companies will stop developing drugs to help people like me if they are not used.	Thank you for your comment. The committee noted that people with the condition have to reduce work commitments and may be unable to continue their usual daily activities. It also noted the loss of confidence and depression that this causes, and that people feel the condition reduces what they are able to contribute to society (see section 3.1 of the FAD). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
82	Public	Carer 6	Being the carer of someone with PPMS, I was disappointed with the recent decision	Thank you for your comment. The committee

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			not to allow the use of ocrelizumab for patients with this type of MS, particularly as I have taken note of its progression through Europe and its acceptance for Relapsing Remitting MS. More so, it is even more disappointing inasmuch that ocrelizumab is the only "real treatment" available for PPMS, which can actually slow down the progression of the disease, as all other things/drugs, called treatments, which have been made available so far, only actually deal with "symptom management" of PPMS. As ocrelizumab is the only drug available to have any chance of slowing down PPMS, you would think that this drug would have been made a "priority" for those with PPMS, rather than those with RRMS, as patients with RRMS have many more drugs available to help them live and cope with their disease and without this treatment PPMS patients will undoubtedly develop into serious disability, in the majority of cases. Having a Law degree, I also believe to allow ocrelizumab for one type of MS and not the other type is discriminatory, inasmuch as those with PPMS have no real treatments available to slow down their disability progression, whereas those with RRMS seem to have lots of treatments available. As a carer of someone who is on the Expanded Disability Scale, already scoring 6.0, having only been diagnosed with PPMS three years ago, the only way forward which I can see without ocrelizumab is one of my partner suffering from severe disability, a way which would be at least slowed down if ocrelizumab had been passed for PPMS. Though there is obviously a cost factor which NICE has to consider, the cost in real terms of PPMS cannot be under-estimated for patients with the disease. I am watching as my partner is deteriorating and knowing that there is a treatment now available which NICE have refused for PPMS is frustrating, gutting and unfair. As you read this I hope that someone close to you does not have to suffer from this debilitating condition and you do not have to watch them deteriorate as quickly as I have. Ocrelizumab has offered hope to patients with PPMS, hope that until now patients have not even been able to consider; I hope that after consultation NICE will pass ocrelizumab as the benefit in real terms for patients with PPMS is life-changing, a benefit which certainly outweighs the cost.	considered that many people with primary progressive multiple sclerosis eventually need support and care from family members or friends, and that the condition can substantially affect the lives of people with the condition and their families. It also considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition (see sections 3.1 and 3.2 of the FAD for more detail). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision. NICE has appraised the use of ocrelizumab to treat primary progressive and relapsing-remitting forms of multiple sclerosis in separate appraisals. Different evidence has been used to assess how effective ocrelizumab is at treating relapsing remitting multiple sclerosis and primary progressive multiple sclerosis; based on trials done in these populations. Different economic models, provided by the company, have also been used in the 2 appraisals to reflect the differences in disability progression, treatments and costs involved in the care of people with relapsing-remitting and primary progressive forms of multiple sclerosis. The clinical and cost-effectiveness estimates of ocrelizumab in these 2 populations therefore differs. The most plausible cost-effectiveness estimates for ocrelizumab for treating primary progressive multiple sclerosis compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources in all scenarios presented by the company using the approved commercial arrangement.
83	Public	Patient 28	Focus must shift from a pure financial consideration to the quality of life for PPMS patients. They need hope and ocrelizumab provides that and encourages further work overall to find a remyelination solution. If cost benefit is the deciding factor please consider the cost to the NHS of mobility equipment, physio and hospital spaces long term. Ask for patient contribution towards cost of treatment if you want to test patient needs.	Thank you for your comment. The health related quality of life for people with primary progressive multiple sclerosis is considered in the estimates of cost-effectiveness used for decision-making.
84	Public	Patient 29	For 20 years I have had chronic/ relapsing MS.I cannot begin to describe this living	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			nightmare. Please give these people hope for life.	
85	Public	Carer 7	My 32 year old daughter was eventually diagnosed in 2016 with PPMS and was told by a neurologist that he had no treatment to offer her. To be told you have an incurable life changing progressive disease is a shattering experience and now that there is a drug that gives some hope to people with PPMS the NHS needs to be able to offer this. Without any treatment people with this disease will deteriorate and become a massive burden to health and social services in the future. It must be more cost effective to offer a drug which has a chance of delaying the progression of disability than to offer nothing. My daughter has embraced diet, lifestyle and exercise but we are realistic that these only help to a degree. My daughter and others like her desperately need to be offered this drug so they have some hope for a future.	Thank you for your comment. The committee considered that many people with primary progressive multiple sclerosis eventually need support and care from family members or friends, and that the condition can substantially affect the lives of people with the condition and their families. It also considered the impact on loss of confidence and depression that living with the condition causes, and noted that ocrelizumab has provided hope of slowing disease progression for people diagnosed with this condition (see sections 3.1 and 3.2 of the FAD for more detail on committee considerations). The committee considered patient and carer perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
86	Public	Public 16	Thank you for the opportunity to comment on your interim decision regarding the use of ocrelizumab for the treatment of primary progressive multiple sclerosis. The MS International Federation (MSIF) is the world's only global network of MS organisations. The movement is made up of 49 MS organisations, with links to many others around the world. MSIF and its members campaign for increased awareness of the disease, support scientific developments and work to improve access to treatments and healthcare. Through capacity building, information and resources, MSIF supports and collaborates with organisations in countries where there is limited provision for people with MS. The global MSIF movement works together to improve the quality of life of everybody affected by MS. You will be well aware that technology appraisal determinations by NICE not only have great impact on the use of treatments in the UK, but carry great weight around the world, with many countries using NICE judgments at least as part of their own determinations on what treatments should be covered for reimbursement. Hence MSIF is interested in your decision on ocrelizumab not only for people with MS living in the UK, but around the world. **Unmet Need** There was great excitement around the world when the trial results for ocrelizumab were published. People with primary progressive MS (PPMS) at last had hope that their debilitating disease could at least be slowed and their quality of life preserved. Then came better understanding of the probable significance that there was a sub-group of people with radiological evidence of inflammation who responded particularly well to treatment and on that basis the marketing authorisation was	Thank you for your comment. The committee noted the unmet need for disease-modifying treatments for this condition, and the substantial effect that is has on the lives of people with the condition and their families (see sections 3.1 and 3.2 in the FAD for further details of committee considerations). It considered patient and carer

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			granted only for that sub-group. That of course left many people with PPMS disappointed, but on the other hand targets ocrelizumab where it can do most good. We hope that, after considering the feedback of stakeholders you will reach a revised decision so that people with PPMS, where there is also evidence (through MRI) of features characteristic of inflammatory activity can access ocrelizumab through the NHS. The number of people who could benefit (in the UK) is not large in number, but this is the only currently licensed therapy that can slow or stop their disease.	perspectives and the unmet need for disease-modifying treatments for this condition alongside the evidence on clinical and cost-effectiveness when making its decision.
			Treating inflammatory damage and optimising medicines Critical to the appraisal of ocrelizumab is an understanding of the primary disease mechanism being treated – auto-immune mediated inflammatory damage. Your appraisal accepts that ocrelizumab would be targeted at the sub group of people with PPMS with inflammatory damage, in line with the marketing authorisation. This is a real attempt at medicines optimisation, using the trial evidence to target the people who could benefit most. That is good for the people being treated, good for stretched healthcare services and good for taxpayers. Companies should be encouraged to break trial data down in this way. With the sub-population in mind, it is important when considering what constitutes the comparator of best supportive care to understand that the management of PPMS with evidence of inflammatory damage should not be regarded as being the same as the general PPMS population. Healthcare beyond pharmaceuticals should of course also be optimised. This is important as your interim appraisal seemed to put some weight on the argument that the NHS would face increased cost from a treatment regime for this population, not only through the drug costs, but through an increase in MRI scanning. The point being that people with PPMS were not thought to currently warrant regular MRI scans. However, for the sub-group of people whose inflammatory damage can be investigated, regular MRI should be considered best supportive care, especially as the imaging evidence can now make a difference to clinical management. Progress in imaging technology that enables the segmentation of a patient population, to better target treatment, should be embraced by NICE and medical practice generally. Therefore, for this sub population, MRI scans should not be considered an additional cost burden, but good practice disease monitoring.	The committee heard from a patient expert at the first appraisal committee meeting that repeated MRI scans are not currently done to monitor inflammatory activity because no disease-modifying treatments are available for primary progressive multiple sclerosis. The committee also noted that the company had included the costs of additional MRI scans related to use of ocrelizumab in its economic model. The committee concluded that the use of ocrelizumab could result in increased demand for MRI scans (see section 3.3 of the FAD for further detail).
			Outcome Measures and Quality of Life There is broad agreement that outcome measures for the treatment of MS need to be improved to better capture the heterogeneity of how the disease affects people and how those affects change over time. Innovation in this area should therefore be welcomed. For this appraisal there is the added impetus for innovation that the traditional focus (in MS treatment trials and consequent appraisals) on incidence of	The committee noted that upper limb function was an exploratory endpoint in ORATORIO and questioned why the company had selected this outcome to include in the model rather than the many other exploratory endpoints measured. The committee heard from the

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			clinically significant relapses (a surrogate for disease activity) are not appropriate. For this appraisal, measures of various aspects of physical and emotional disability and impairments would inevitably need to be different to older RRMS submissions. Going beyond EDSS is a very positive step for the assessment of MS treatments. EDSS puts great weight on walking ability, which is certainly important, but underestimates other symptoms and functions. We were surprised therefore to see the interim appraisal rejected the added weight given in the ocrelizumab application to fatigue and upper limb function. In the case of fatigue, this consistently comes out as one of the most significant symptoms for people with MS. Hence the James Lind Alliance Priority Setting Partnership rated it as the most important symptom in their exercise to establish research priorities for MS. Fatigue also featured prominently in a similar exercise run by MS Research Australia. It was the most prevalent symptom in the MS in America Survey. And it was the top symptom in an American iConquerMS study looking at the key quality of life factors for people with progressive MS. Upper limb function is harder to evidence in this way, though mobility generally also features very highly in the exercises and studies described above. Then we should consider the question of how people with MS adapt to specific impairments, or don't. It is well known that people can adapt to disability and live higher quality lives than healthy people believe is the case. It is equally clear that some impairments (and symptoms) are harder to adapt to. Limited upper limb mobility is certainly extremely challenging, with impacts on every area of life and notably on self-care. Independence and the ability for self-care is hugely important to quality of life in people with MS, with obvious consequences for mental health too. Furthermore, the self-care aspect in this context has the added importance of being a key factor in driving up personal care costs. So when reconsidering this appraisal we hope that the Committee will reconsider the weight given to fatigue and upper limb function in the ocrelizumab application. **Summary** Ocrelizumab is an effective treatment for auto-immune mediated inflammatory damage. As well as having proven efficacy in relapsing forms of MS, it is a breakthrough product in also having proven efficacy at least for a segment of the primary progressive MS population. We hope that NICE will reconsider the aspects of the appraisal covered above and come to the conclusion that the treatment offers a hope for people with PPMS, but is also a good deal for the National Health Service and for taxpayers. We also hope that other appraisal authorities around the world take note of the special factors in this case and make ocrelizumab available, in a targeted way, through systems of reimbursement.	ERG that the measure of upper limb function used in ORATORIO (changes in time to complete the 9-hole peg test) may not reflect changes in upper limb function that matter to people, such as reduced ability to wash, dress and feed themselves. The committee objected to using chosen selected exploratory endpoints in the modelling without considering the risk of false-positive findings. The committee still considered at its second meeting that including decrements for upper limb function, decreasing utilities as people progressed through EDSS states, and carer disutilities likely overestimated the effect of ocrelizumab on slowing disability progression. It concluded that it was inappropriate to include utility decrements from upper limb dysfunction in the economic model. Section 3.16 of the FAD has been amended to reflect this.

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 19/07/2018. Email: TACommB@nice.org.uk or upload to NICE Docs

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Roche Products Ltd**; hereinafter “Roche”
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

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Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Summary	Roche appreciates the opportunity to provide comments on the NICE Appraisal Consultation Document (ACD) for *'Ocrelizumab for treating primary progressive multiple sclerosis [ID938]'*. While disappointed that the committee was unable to recommend ocrelizumab in the ACD and did not see a need for the proposed Managed Access Agreement, Roche is committed to exploring all options to ensure ocrelizumab is made available to NHS patients. In the spirit of trying to find a solution we have proposed an alternative commercial offer; however, pending agreement on its implementation we are as yet unable to present it to the Committee for consideration. Given the significant unmet need - with a complete lack of effective treatments that modify the course of the disease - and the current inequity between people with different forms of MS, we ask for greater flexibility to be applied that would allow consideration of the proposed commercial arrangement and demonstration of plausible cost-effectiveness. We therefore request that all relevant stakeholders (including NICE, NHSE and Roche) meet to discuss potential pragmatic mechanisms that would permit access to this innovative medicine for people with early PPMS. Roche has submitted an appendix with new evidence from the open label extension (OLE) period of the pivotal phase 3 ORATORIO study. These new data were not available until after the first appraisal committee meeting, and address the uncertainty around the size and durability of treatment effect, as raised by the committee in the ACD. The OLE data represent the longest duration of continuous data available for ocrelizumab (6 ½ years of follow-up). In addition, Roche has submitted an appendix with results of a revised base case using the following modelling assumptions preferred by the committee: • CDP-24 used as the measure for disability progression • Cost and disutilities of relapses included • Risk of progressive multifocal leukoencephalopathy (PML) for ocrelizumab included (using data from rituximab in rheumatoid arthritis as proxy, similar to the approach in the recent NICE appraisal for ocrelizumab in relapsing MS, ID937) • Utility decrement for fatigue excluded • 50% waning after 10 years included (uncertainty was highlighted by the committee, concluding that true waning likely lies between an assumption of no waning and an

	assumption of 50% waning after 5 years. Based on the durability of effect observed in OLE data, we propose that waning is assumed to start after 10 years [in line with recent RRMS MTA TA527], see below) • UK MS Survey used as the source of EDSS costs (in line with committee's conclusion that EDSS costs are the same in RRMS and PPMS, similar to the approach used in the recent NICE appraisal for ocrelizumab in relapsing MS, ID937) • Stopping rule of EDSS ≥7 used (in line with Roche's understanding of the ACD, uncertainty highlighted by the committee) • 50% increased stopping rates after 5 years used, as proposed by the ERG (uncertainty highlighted by the committee) However, Roche believe that several conclusions in the ACD are not a reasonable and fair interpretation of the evidence and encourage the committee to reconsider its conclusions. The responses below address these themes in turn: 1. Effect size and durability 2. Utility decrements for upper limb dysfunction 3. Health state utility values 4. Treatment waning, treatment duration, and stopping rules 5. MSBase registry data 6. Proposed commercial arrangement The revised base case analysis presented in the appendix therefore includes the following modelling assumptions preferred by Roche: • CDP-24 effect size from crossover adjustment of OLE (new evidence) • Health state utility values from ORATORIO study used to reflect the population with early PPMS with inflammatory activity • Utility decrements for upper limb impairment included The impact of some of these assumptions and inputs is explored further in scenario analyses (see appendix).
1	**Ocrelizumab treatment effect** The ACD states in 3.22 that *'Ocrelizumab slows disability progression compared with placebo, although the size and duration of the effect are uncertain.'* Roche would like to make the committee aware of new data supporting the long-term efficacy of ocrelizumab in PPMS, which provides additional evidence of the treatment duration and effect size. Patients completing the phase III ORATORIO study could enter an OLE period following unblinding of study centres, which started when the study was ascertained to be positive (initiated 12th Oct 2015). Upon completion of the ORATORIO double-blind placebo-controlled period, patients remained blinded and on-treatment as originally assigned for an additional extended controlled treatment period (ECP) ranging from the clinical cut-off date (24th July 2015) until the first dose of OLE, and was completed

	when the last patient entered the OLE (27th April 2016). The most recent data cut-off from the OLE extends to Week 336 (5th February 2018) (i.e. nearly 6 ½ years of follow-up). Upon entering the OLE, patients previously receiving placebo switched onto ocrelizumab. To estimate comparative long-term treatment effect versus placebo during the OLE, crossover was adjusted using the Rank Preserving Structural Failure Time (RPSFT) model. This methodology is endorsed by the NICE DSU document TSD16 (1) and has been employed in many previous oncology NICE appraisals as well as a recent RRMS appraisal (2) to estimate treatment effect during OLE periods. RPSFT produces a counterfactual data set, adjusting the survival estimate in the presence of treatment switching in order to provide an estimate of the survival times that would have been observed in the absence of switching. This type of crossover adjustment method assumes a common treatment effect, whereby the treatment effect received by those switching from placebo to ocrelizumab is assumed to be the same as the treatment effect received by those initially randomised to ocrelizumab. Clinical advice was sought at a recent advisory board organised by Roche to assess the validity of this assumption. Clinical experts considered this assumption to be valid as switching upon entering the OLE was not dependent on progression and hence the risk of progression can be considered equal between the time of randomisation and time of entering OLE/switching. An alternative method of crossover adjustment, inverse probability of censoring weighted (IPCW), necessitates the use of longitudinal data on covariates and patient characteristics which predict treatment switching and prognosis. This information was not collected in ORATORIO OLE and therefore an IPCW model cannot be applied to the dataset to adjust for crossover. For the above reasons we therefore believe the RPSFT crossover adjustment is a valid method to estimate the long-term treatment effect of ocrelizumab. The robustness of the crossover adjustment was assessed in sensitivity analysis and the consistency of OLE results was assessed by comparing results across different disability outcomes (CDP-12 and 9-HPT). The risk of selection bias was considered minimal in the OLE study, as very few patients chose not to enter the OLE study (see Appendix). The most common reason recorded for not entering the OLE was ‘completed study’. In addition, no pattern for reasons of censoring could be discerned between pre- and post-OLE entry in the cohort of patients switching from placebo to ocrelizumab. <u>New evidence from OLE study in MRI active population</u> Analysis of the OLE data over 6 years indicated that the treatment effect size for ocrelizumab in the MRI active population further increases past the initial controlled treatment period. This increased treatment effect was consistently observed when a different disability outcome was assessed, CDP-12 (see Appendix). The size of treatment effect on upper limb function remained largely stable over time. Sensitivity analysis indicates that the crossover-adjusted effect size is relatively insensitive

	to different analysis methods and assumptions (see Appendix). The phenomenon of a lag time before reaching maximal treatment effect size on disability outcome measures has been observed in other trials of anti-inflammatory DMTs in progressive forms of MS (3). A biological mechanism has been proposed to explain the observed therapeutic lag of effect on disability accumulation with anti-inflammatory therapies, such as ocrelizumab, in progressive forms of MS. This lag may be explained by the delayed neurodegeneration induced by prior inflammation and can be compounded where there is limited neuronal reserve left to compensate for this damage (4). The low neuronal reserve for lower extremity function may lead to a long delay between anti-inflammatory intervention and therapeutic benefit on EDSS progression. Therefore, it may take several years for the effect of an anti-inflammatory DMT on lower limb disability to become clinically apparent. The increased treatment effect size for ocrelizumab with regards to CDP-24 and CDP-12 appears to follow the pattern predicted by this hypothesis (see Appendix). Furthermore, as upper limbs are typically affected at a later stage of the disease than lower limbs (proposed to be explained by the decreased likelihood of a lesion in shorter length central axons projecting towards the upper limbs vs. lower limbs – known as the length-dependent MS axonopathy hypothesis, as well as the observation that the region of the spinal cord most commonly damaged is below that which serves the upper limbs), it is anticipated that they will have accrued less damage and retain higher reserve capacity. Therefore, not only is the subsequent clinically apparent disability less significant but also the retained reserve can compensate for any damage that does occur (4-8). Consistent with this, the maximum treatment effect of ocrelizumab on upper limb function is achieved after a shorter period of time i.e. without a significant lag, as more of the effect is acting on current or recent inflammation with less delayed neurodegeneration to effect and therefore consistent with higher neuronal reserve. Consequently, the treatment effect size for 9-HPT remains constant through the OLE (see appendix).
2	**Utility decrements for upper limb dysfunction** The committee concluded in 3.15 of the ACD that it is not appropriate to include additional utility decrements for upper limb dysfunction. The reasons given were the following: • *The ERG highlighted that previous appraisals for multiple sclerosis had not used specific utility decrements for symptoms.* • *The clinical experts commented that upper limb function are equally important for people with relapsing–remitting multiple sclerosis.* Roche is particularly concerned by this conclusion and believe it contradicts section 3.2 of the ACD which recognises the pivotal role of upper limb function in maintaining patients' independence. We would like to reiterate the importance of upper limb function to patients with MS, and refer to a recent survey which indicated that a majority of patients with MS in the UK (88%) considered upper limb function to be more important than lower limb

	function (9). Upper limb dysfunction is not a symptom, instead it is an important component of multi-dimensional disability in PPMS that is not adequately captured by EDSS. Manual dexterity is an important predictor of overall activity and participation within the community – upper limb dysfunction in MS contributes to a reduced ability to perform activities of daily living, resulting in decreased independence and quality of life [58]. Dysfunctions of the upper extremities occur in at least 66% of people with MS, and approximately 44% experience problems with activities of daily living [59]. Furthermore, utility decrements for upper limb dysfunction should not be excluded from the model because they have not been incorporated in economic models of RRMS to date. Our understanding of all forms of MS continues to evolve and there is a growing appreciation of the impact of upper limb function on patients' independence and health-related quality of life (HRQoL). Therefore, we urge the committee to permit advancements in the understanding of a disease to be acknowledged and reflected in this appraisal. Whilst we agree that maintaining upper limb function is important for both people with RRMS and those with PPMS, it is more ***relevant*** for people with PPMS. This is due to the longer time to diagnosis for people with PPMS, and subsequently these patients often already have significant lower limb disability and are closer to being in a wheelchair at the point when treatment can potentially be initiated compared to those with RRMS. Consequently, preserving upper limb function is a more relevant treatment goal for people with PPMS. The non-linearity of the EDSS scale means that it is less sensitive to increasing disability at later stages of disease. Conversely, the 9-HPT provides greater precision, i.e. it captures upper limb disability progression occurring between higher EDSS states. Therefore, measurements of the impairment of upper limb functions give important additional information about patients' level of disability affecting their HRQoL, that is not adequately captured by EDSS alone. The impact of upper limb impairment on patients' HRQoL was quantified by evidence from the ORATORIO study in PPMS. Multivariate regression analysis of EQ-5D data collected in the trial indicated that upper limb dysfunction affected HRQoL ***independent*** of EDSS state. After controlling for EDSS at later stages of disease (EDSS ≥5), upper limb impairment led to a reduction in utility of −0.064 (p=0.013). The regression analysis followed a similar approach to Orme et al (2007) (10) which reported utility decrements for relapses and disease type (RRMS, SPMS, PPMS) and has been used in previous NICE appraisals in RRMS. The latest study published by the same research team reported utility decrements for fatigue and cognitive impairment independent of EDSS in patients with MS (11). Upper limb function was not measured in this study. The ORATORIO trial evidence provides a unique dataset of patients with PPMS in which upper limb function was measured (using 9-HPT) alongside patient-reported HRQoL

	(using EQ-5D), and is therefore the first study to demonstrate the independent effect of upper limb dysfunction on HRQoL in patients with MS (12). For all these reasons, we strongly believe that the importance of upper limb function should be translated into QALYs and that it is therefore appropriate to include utility decrements of upper limb dysfunction in the economic model, and we encourage the committee to reconsider their conclusion.
3	**Health state utility values** The committee concluded in 3.14 of the ACD that utility values from Orme et al (2007) were preferred. The reasons given for this are the following: • *The committee noted that the population that its recommendations would apply to would include people aged over 55 years who are not represented in ORATORIO.* • *also preferred using utility values from a single source, rather than using different sources for different EDSS states.* Roche does not agree with this conclusion and believe it needs contextualisation. The marketing authorisation for ocrelizumab is in early PPMS with inflammatory activity. As shown in Figure 14 in our response to clarification questions, evidence from the ORATORIO study demonstrated there is a trend of decreasing inflammatory activity with age. This is likely explained by the underlying pathology of the disease course in PPMS shifting from an inflammatory to a primarily neurodegenerative process. As such, patients with inflammatory activity tend to be younger and we would not expect many patients over 55 years to be eligible for treatment with ocrelizumab. The utility values described in Orme et al (2007) were elicited from people with PPMS, not specifically early PPMS with inflammatory activity. The average age in Orme et al (2007) (51 years for the full cohort of patients with MS, average age for the sub-cohort with PPMS unknown) was considerably higher than that in the ORATORIO study (44 years). Based on the trend observed in ORATORIO, it can be speculated that not many patients with PPMS in Orme et al (2007) had inflammatory activity. As such, the characteristics of this patient cohort may be fundamentally different from the one that matches eligibility for treatment with ocrelizumab. The utility values from the ORATORIO study are therefore more appropriate to apply in the economic model as these reflect the population that the NICE recommendation would apply to. In addition, in previous appraisals in RRMS the committee preferred using utility values from clinical trials supplemented with Orme et al (2007) for the highest EDSS states not included in the trials, and we see no reason for a different approach in PPMS. Although it is not ideal to mix different sources for utilities, the trial should be considered the best available evidence to reflect people with early PPMS with inflammatory activity.
4	**Treatment waning, treatment duration, and stopping rules**

	The committee concluded in 3.11 of the ACD that *'treatment efficacy may wane over time with ocrelizumab, but the absolute rate of waning is uncertain. The committee concluded that the company's assumption of no waning of treatment effect was too optimistic, but that the ERG's approach may be too pessimistic. It concluded that the true waning of treatment effect is likely to lie between these 2 approaches.'* Furthermore, the committee states in 3.12 of the ACD that *'including both stopping and, separately, waning in the ERG's base case may have overestimated the rate of stopping treatment. It concludes that there is considerable uncertainty about how long people would continue to take ocrelizumab.'* Roche would like to refer the committee to the latest analysis from the OLE study (see above and in the appendix) which demonstrates a sustained effect during 6 ½ years of follow-up. OLE data supports lack of a waning effect during this period, and therefore we believe the ERG scenario of assuming a 50% drop in efficacy after 5 years to be implausible. Furthermore, ocrelizumab is associated with very low incidence of anti-drug antibodies (see company submission). This is due to the relatively low immunogenicity profile associated with humanised antibodies. The presence of anti-drug antibodies correlates with reduced efficacy of other DMTs in MS (13-18). As such, the negligible proportion of patients treated with ocrelizumab developing neutralising antibodies suggests they cannot be a source of treatment waning for ocrelizumab. Waning may be hypothesised to occur when the underlying disease course is no longer driven by inflammatory processes. There is a lack of evidence about when this occurs in PPMS, and cannot be monitored by MRI whilst on treatment because ocrelizumab causes near-complete (>95%) suppression of MRI activity. As such, it is important for clinicians and patients to monitor clinical events of progression on multi-dimensional aspects of disability and to agree when to stop treatment. Roche believes that a consensus of the clinical community about stopping criteria could allow management of patients' expectations. We agree with the committee's conclusion that including both stopping and waning may be considered double counting. The committee concluded in the ocrelizumab in RRMS appraisal (ID937) that stopping rates could be considered proxies for waning rates, and we believe this principle to be relevant in PPMS as well. We do not agree with the committee's assertion that including both waning and stopping rates may have overestimated the rate of stopping. This implies that more patients would continue treatment despite the presence of waning. We do not believe this to be plausible and would argue instead that including both stopping and waning rates likely overestimates the rate of waning, as patients would be expected to stop if they no longer derive the expected benefit from treatment. Despite the above concerns about double counting, we propose in our revised base case for PPMS a waning effect of 50% after 10 years. We believe this to be conservative as our

	OLE study provides evidence of sustained long-term effect. However, this waning assumption is in line with the one used by NICE in the recent MTA for beta-interferons and glatiramer acetate (2). The impact of assuming no waning or not applying increased stopping rates is explored in a scenario analysis.
5	**Natural history of early PPMS** The ACD states in 3.10 that '*The clinical experts commented that a lot of data in the MSBase registry come from Eastern Europe, where the definition of primary progressive multiple sclerosis may differ from the UK. The committee concluded that it had concerns about using data from the MSBase registry to inform baseline transitions between EDSS states in the absence of treatment in the company's model, and considered that its use was associated with uncertainty*.' Roche would like to clarify that the MSBase analysis was a bespoke project for this submission. The cohort used to derive transition probabilities matches the ORATORIO inclusion criteria to mimic early PPMS, and is not the full PPMS dataset in the MSBase registry. Canada, Spain, Italy, Netherlands and Australia are the top 5 countries that contributed to this analysis and accounted for 80% of the early PPMS analysis set (data on file). These countries' healthcare systems are similar to the UK and are expected to adhere to similar definitions of PPMS diagnosis and treatment. We therefore expect the MSBase PPMS cohort to not significantly differ from the UK PPMS population, and for the transition probabilities in the model to be appropriate. The MSBase registry currently represents the best available evidence of natural history in PPMS. As explained in the company submission, other registries were contacted but their datasets did not contain the necessary depth and completeness in PPMS to derive transition probabilities for the economic model. Likewise, the placebo arm of the ORATORIO study contained fewer data points (fewer patients and shorter follow up duration than the registry), which would have introduced more uncertainty. As exemplified by previous NICE appraisals in RRMS, registry data is preferable to trial data for deriving long-term natural history.
6	**Proposed commercial arrangement** The committee noted in 3.17 of the ACD that '*the company presented a proposal for a commercial arrangement. It stated that this would provide ocrelizumab to the NHS at a reduced price (which is commercial in confidence) until an ongoing trial finishes'*. Roche would like to clarify that the proposed commercial arrangement would be expected to apply not only during the period of data collection but indefinitely, unless a future NICE re-review of this appraisal warrants a review of the arrangement with the NHS.
Conclusion and updated results	An updated base case is provided in response to this ACD which reflects many of the committee's preferences, as discussed above. However, inputs for health state utility values and inclusion of utility decrements for upper limb dysfunction are based on

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	company's preferences, as explained in earlier sections of this response. A number of scenario analyses have been conducted to explore the impact of uncertainty around a number of modelling assumptions. Full details can be found in the Roche ACD response appendix; however, a summary is provided below. New base case analysis The updated base case results in a QALY gain of [redacted] with ocrelizumab treatment, compared with [redacted] QALYs with BSC. The resulting incremental ICER for ocrelizumab compared with BSC is £62,766 based on the approved PAS for ocrelizumab, without consideration of the proposed commercial offer. New scenario analyses Additional scenario analyses explored the impact of different parameters and inputs. The results were particularly sensitive to the source of efficacy (i.e. double blind trial period only, or including open label extension period). In addition, source of health state utilities values and impact of upper limb function were key drivers of the model. Finally, the results were sensitive to clinical uncertainties highlighted by the committee in the ACD, i.e. waning assumption and treatment duration. We ask the committee to consider the lack of treatment options in PPMS, the inequity between people with different forms of MS, and the innovative nature of ocrelizumab, as highlighted in the ACD. We hope that further discussions are enabled with all relevant stakeholders (including NICE, NHSE and Roche) to discuss potential solutions to allow Roche's commercial offer to be taken into consideration. Together with the revised base case assumptions, we believe that greater flexibility around implementation of commercial arrangements would enable people with early PPMS with inflammatory activity to have access to ocrelizumab in the NHS.

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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References

1. Latimer NR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching 2014 [Available from: http://www.nicedsu.org.uk/TSD16_Treatment_Switching.pdf.
2. National Institute for Health and Care Excellence. Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809] 2018.
3. Tur C, Montalban X, Tintore M, Nos C, Rio J, Aymerich FX, et al. Interferon beta-1b for the treatment of primary progressive multiple sclerosis: five-year clinical trial follow-up. Arch Neurol. 2011;68(11):1421-7.
4. Giovannoni G, Cutter G, Sormani MP, Belachew S, Hyde R, Koendgen H, et al. Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses. Mult Scler Relat Disord. 2017;12:70-8.
5. Krieger SC, Sumowski J. New Insights into Multiple Sclerosis Clinical Course from the Topographical Model and Functional Reserve. Neurologic clinics. 2018;36(1):13-25.
6. Sandroff BM, Schwartz CE, DeLuca J. Measurement and maintenance of reserve in multiple sclerosis. J Neurol. 2016;263(11):2158-69.
7. Sumowski JF, Rocca MA, Leavitt VM, Meani A, Mesaros S, Drulovic J, et al. Brain reserve against physical disability progression over 5 years in multiple sclerosis. Neurology. 2016;86(21):2006-9.
8. Weier K, Mazraeh J, Naegelin Y, Thoeni A, Hirsch JG, Fabbro T, et al. Biplanar MRI for the assessment of the spinal cord in multiple sclerosis. Mult Scler. 2012;18(11):1560-9.
9. Dubuisson N, Baker D, Thomson A, Marta M, Gnanapavan S, Turner B, et al. Disease modification in advanced MS: Focus on upper limb function. Mult Scler. 2017;23(14):1956-7.
10. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 2007;10(1):54–60.
11. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler. 2017;23(8):1123-36.
12. Daigl M, Bennett I, McDougall F, Singh Jhuti G, editors. Impact of Disease Activity Measures on Health Utilities in Primary Progressive Multiple Sclerosis. International Society for Pharmacoeconomics and Outcomes Research; 2017.

13. Calabresi PA, Giovannoni G, Confavreux C, Galetta SL, Havrdova E, Hutchinson M, et al. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. Neurology. 2007;69(14):1391-403.
14. European Medicines Agency. Scientific Discussion: European Public Assessment Report - Tysabri. 2006.
15. Fox EJ, Vartanian TK, Zamvil SS. The immunogenicity of disease-modifying therapies for multiple sclerosis: clinical implications for neurologists. The neurologist. 2007;13(6):355-62.
16. Kappos L, Clanet M, Sandberg-Wollheim M, Radue EW, Hartung HP, Hohlfeld R, et al. Neutralizing antibodies and efficacy of interferon β-1a. A 4-year controlled study. 2005;65(1):40-7.
17. Vartanian TK, Zamvil SS, Fox E, Sorensen PS. Neutralizing antibodies to disease-modifying agents in the treatment of multiple sclerosis. Neurology. 2004;63(11 Suppl 5):S42-9.
18. Vennegoor A, Rispens T, Strijbis EM, Seewann A, Uitdehaag BM, Balk LJ, et al. Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis. Mult Scler. 2013;19(5):593-600.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	MS Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	**Unmet treatment need** Primary progressive MS represents a huge unmet need in MS treatment with no disease modifying treatments currently available on the NHS. People affected by primary progressive MS are, understandably, feeling incredibly let down by NICE's appraisal consultation document recommendation. There are now 13 licensed disease modifying treatments on the NHS for people with relapsing MS offering a range of efficacy levels, side effects and ways to take a treatment. Yet ocrelizumab is the only licensed disease modifying treatment option for primary progressive MS. People have watched and waited while licensed treatments for relapsing MS have rapidly increased and becoming more effective and easier to take, pinning their hopes on ocrelizumab as potentially their first NHS treatment. While NICE have acknowledged the importance of ocrelizumab and the concerns of people with primary progressive MS they have not gone as far as to recommend that it is used on the NHS. It is vitally important to people affected by primary progressive MS that ocrelizumab is approved by NICE for as many people as possible.
2	**The importance of factoring in upper limb function** For primary progressive MS where relapse rate is less of an indicator for clinical effectiveness it is important to consider any available evidence of treatment effect. People with primary progressive MS have written to us of the importance of maintaining as high a degree of independence as possible. As a person's disability progresses the importance of upper limb function increases as people become increasingly dependent on it to maintain a level of mobility and independence. Common measures of disability in MS including EDSS have been described as "insensitive to change at the higher end" by the Nuffield Trust in a recent report commissioned by the MS Society[1], which means disability progression such as upper-limb function may be undervalued in terms of utility decrement. At the committee meeting the clinical experts were asked if upper limb function should be looked at as a separate utility decrement when it is not usually in relapsing MS appraisals. Within this context the clinical experts agreed it shouldn't be treated as more important in people with primary progressive than relapsing MS, and the issue was not revisited by the committee. If the committee had asked the clinical experts whether greater importance should be placed on upper limb function in appraisals generally they would have likely given an affirmative answer.

[1] Castle-Clarke S, Curry N, Dorning H and Wetherly L (2018) Improving care for people with MS: the potential of data and technology. MS Society. Report www.nuffieldtrust.org.uk/research/improving-care-for-people-with-ms-the-potential-of-data-and-technology

	Trials for relapsing MS have focused predominantly on annual relapse rate as a primary end outcome but the importance of the 9 hole peg test in MS clinical trials is only now being fully acknowledged as more research aims to assess the impact of DMTs on upper limb function. This is something that the EMA have already accepted in principle.[2] NICE should consider all evidence which has been submitted to them when modelling ocrelizumab's effectiveness in primary progressive MS and in particular adding utility decrements to reflect the full importance of upper-limb function in MS. NICE acknowledging the importance of capturing upper limb function in this way would show strong leadership and ensure that more people with MS are able to take part in clinical trials in the future.
3	**Stopping criteria** Currently treatments for MS in England are stopped when someone reaches EDSS 7.0 and require the use of a wheelchair. This is due to the clinical trial eligibility not including wheelchair users. Many clinicians, having witnessed their patients relapsing when taken of treatment, are concerned over the impact the stopping criteria is having. As set out above the use of EDSS 7.0 as a stopping criteria reflects the undue prominence given to mobility over upper limb function in previous clinical trials, rather than specific evidence that DMTs are not effective beyond this point of progression. We therefore agree with the clinical expert that continuing treatment to an EDSS stage of 8.0 (or potentially 8.5, which is the point at which upper-limb function has deteriorated) is more appropriate. This broadly maps onto the trial population in the sense that starting criteria went up to 6.5 and the definition of clinical progress was an increase of 1 point on the EDSS scale (but some people saw greater increases).
3	**Importance of innovation** The appraisal consultation document acknowledges that ocrelizumab is an innovative new treatment which marks a 'step change' in treatment for primary progressive MS. This needs to be taken into full consideration when factoring in the levels of uncertainty within the models analysed by NICE. The MS Society would like to see steps taken to ensure that ocrelizumab is made available to as many people eligible as possible. We would like to see NICE and Roche work together to reach a compromise which allows people with primary progressive MS to access this innovative new treatment.
4	**Wider impact on carers/societal benefits** For those who are still in work the fear of having to retire early and to seek financial support is a particular worry. A point raised by many people with MS in support of our previous

[2] https://pharmaphorum.com/news/ms-drugs-needed-preserve-hand-function/

	submission as to why they want ocrelizumab was to help keep them providing for themselves and their family. As primary progressive MS is typically diagnosed in people in their forties, many people have young children. We have heard from numerous people and their carers who speak of how difficult they find it to be dependent on their family to help care for both them and their children. People with MS often need support from family and/or friends to help them to manage the impact of having MS, to help them remain independent and lead a fuller life. This includes support with everyday tasks like washing and dressing and getting out and about. As disability progresses the need for this support increases and the impact on carers can be greater. Recent research by the MS Society showed that the proportion of people with MS who received care, support or assistance from a friend or family member had increased from 71% to 85% from 2013 to 2016.[3] If people had access to ocrelizumab and were able to decrease the progression of disability there would be less need to rely on support from carers. This was brought up frequently by people who wrote to us in support of this submission, many of whom are concerned about the impact their MS has on their family.
5	**Hope and the impact on mental health** It has been estimated that up to 50% of people with MS experience clinical depression which can have profound effects on a person's quality of life requiring medication and other interventions to treat. The first treatment of its kind, ocrelizumb offers people hope for the future of their condition where it was previously lacking. The impact that hope and optimism for the future can have on mental health is well documented and should be considered as an extra factor by the committee.[4] The negative impact on mental health that being diagnosed with an untreatable progressive condition has cannot be overstated. Some people have commented to us that they hope ocrelizumab will help slow their progression until more effective treatments are established. Other people hope that ocrelizumab could be even more effective than the trials have indicated so far, giving them a chance to get some mobility back so that they can again engage in everyday activities, such as walking to the shops or even to the bathroom without difficulty. Others have more modest hopes that ocrelizumab will slow their disability progression allowing them to stay active for longer so that they can keep providing for their family. For many others the thought of being able to achieve important milestones in life that they currently feel will be impossible is inspiring. As we highlighted in our previous submission people spoke of "maybe being able to walk my daughter down the aisle one day", or about taking "my son to football matches without worrying how far I would have to walk". People with progressive MS have seen the innovation and progress that has been achieved in treating relapsing MS since beta interferons and glatiramer acetate were first conditionally approved in the risk sharing scheme and they hope that an approval for ocrelizumab could lead to similar benefits.

[3] Wallace, L., Cavander- Attwood, F., Redfern-Todts, D. Social care and the MS community in England 2016
[4] Conversano, Ciro et al. "Optimism and Its Impact on Mental and Physical Well-Being." *Clinical Practice and Epidemiology in Mental Health : CP & EMH* 6 (2010): 25–29. *PMC*. Web. 16 July 2018.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Multiple Sclerosis Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]
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1	The MS Trust is extremely disappointed that NICE is unable to recommend ocrelizumab as an NHS treatment for early primary progressive MS with imaging features characteristic of inflammatory activity.
2	**Huge unmet need** While we recognise the difficulties posed by this appraisal, we wish to emphasise the huge unmet need for a treatment which will slow down progression in primary progressive MS (PPMS). Our announcement of NICE's initial decision to reject ocrelizumab for PPMS was greeted by bitter disappointment from our supporters. Before preparing our appraisal submission to the committee, we conducted a survey to gather the views of those affected by PPMS. We received nearly 500 responses (31 January – 14 February 2018) from people with PPMS, their families and specialist MS health professionals. Time and again respondents to our survey commented that there is currently no treatment to delay the progression of PPMS, nothing that can change the prognosis of their condition. Many people are doing all that they can to minimise the impact of PPMS, but they are all too aware that there is nothing that will slow down the progression of their disease. The overwhelming majority of people with PPMS are delighted that there is, at last, potential to slow down the progression of their condition; over the years as the number of treatments available for relapsing MS have grown, people with progressive MS have felt that their needs have been forgotten. Many respondents to our survey recognised that their PPMS may be too advanced to gain a benefit, but believed others should be given the opportunity to take a medication that would improve their prognosis and quality of life. The benefits of slowing down progression are seen as maintaining mobility and independence for longer, allowing people to continue to work for longer, and saving costs for the NHS in the long term by preventing progression and the need for MS services and social care.
3	**Primary progressive MS different to relapsing remitting MS** Throughout the ACD, reference is made to appraisals for relapsing remitting MS. We wish to state very clearly that the lived experience of PPMS is very different to relapsing MS. We urge the committee to recognise the significant differences between PPMS and relapsing MS and how they affect someone's daily life, and their outlook for the future. We are very concerned that these differences are properly and fairly reflected in the calculations of cost effectiveness and modelling which are so critical to the outcome of this appraisal. In particular, we note that discussions around the most appropriate utility values for modelling purposes (3.14, page 13) propose using those from Orme et al which groups the different types of MS together. The data from Hawton and Green, 2016 separates out health state utility values (HSUVs) by type of MS – according to both the EQ-5D and the SF-6D, HSUVs were lower for those with progressive MS than for those with relapsing MS, implying that PPMS and secondary progressive MS have a greater impact on health-related quality of life. Can the committee, ERG and manufacturer confirm that the utility values from Orme adequately reflect this difference?

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	In PPMS, disability increases from the outset. The rate of disability progression varies between individuals. For some, disability may progress very gradually, and may remain stable or even improve very slightly over a short period. For others the progression is more rapid and unrelenting. Although the degree of disability will vary, the uncertainty of prognosis is universal. From the early stages of PPMS, quality of life is markedly affected and deteriorates as the disease progresses. People with PPMS are diagnosed later in life leading to complications with co-morbidities. As a result, MS symptoms are more persistent and difficult to manage[1]. A clear consequence of this is a higher mortality rate for PPMS compared to relapsing MS. A recent Norwegian study found that life expectancy for relapsing MS was longer (77.8 years) than for those with PPMS (71.4 years)[2].
4	**Maintaining independence – upper limb function** We are pleased to see that the ACD acknowledges the importance of preserving upper limb function ULF) to allow people to continue working, engage in everyday activities and self-care (3.2, page 5). In our submission to the appraisal, we included quotes from people, all provided unprompted, which illustrate the value people place on hand and arm function: • *if I could preserve my hand function it would mean I could remain mainly independent which would benefit everyone.* • *Although I have limited mobility it is my hands deteriorating that I would like to slow or stop* • *I don't like being with people I don't know. I'm embarrassed because I can't use my hands properly so I have to have food cut up for me and I can't hold a glass or cup properly.* • *I have difficulty preparing meals as I am naturally right handed and I no longer have any strength in my right hand or arm. Also very little strength in my right leg and foot as I have foot drop on that foot. Dressing is also a problem.* Impairment of upper limb function has been completely overlooked in relapsing remitting MS trials, but is a very significant aspect of progressive MS disability. There is a growing recognition of the importance of ULF for many activities of daily living and maintaining independence. EDSS has been criticised for focusing too much on walking ability from 4.0 upwards and does not reflect changes in ULF. In ORATORIO, the nine hole peg test (9HPT), the gold standard for assessing upper limb function[3], was measured throughout the study. A 20% increase in the time taken to complete the 9HPT was used as one of the measures of disability progression, a measure which is widely regarded as a clinically meaningful worsening[4]. Ocrelizumab reduced the time to 24-week confirmed progression on 9HPT by 45% for both hands, 35% for stronger hand and 40% for weaker hand, compared to placebo. The ACD criticises the manufacturer (3.21, page 17) for applying a utility decrement to each EDSS

[1] Holland NJ, et al. Meeting the needs of people with primary progressive multiple sclerosis, their families and the heal-care community. Int J Ms Care 2011;13:65-74

[2] Lunde HBM, et al. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psych 2017;88:621-25

[3] Feys P, et al. The nine-hole peg test as a manual dexterity performance measure for multiple sclerosis. Multiple Sclerosis 2017;23:711-20.

[4] Kragt JJ, et al. Clinical impact of 20% worsening on timed 25-foot walk and 9-hole peg test in multiple sclerosis. Multiple Sclerosis 2006;12:594-98.

	state for people with upper limb dysfunction. We believe this is appropriate as EDSS does not discriminate between changes in ULF. Maintaining ULF and therefore independence for longer clearly represents significant cost savings for the NHS, social care and reduces informal carer burden.
5	**Maintaining independence – mobility** A recent analysis of ORATORIO data has found that ocrelizumab treatment was estimated to delay the need for a wheelchair by 7 years compared to placebo; the median time-to-wheelchair was an estimated 19.2 years for ocrelizumab-treated patients and 12.1 years for the placebo group[5]. Maintaining mobility and therefore independence for longer clearly represents significant cost savings for the NHS, social care and reduces informal carer burden.
6	**Best supportive care** The ACD states that cost-effectiveness estimates for ocrelizumab compared with best supportive care alone are too high (section 1, page 3). Best supportive care is not defined in the ACD, nor are costs provided, so it is impossible for us to comment on the composition and level of NHS services that is assumed to be available across England and Wales. There is currently no research or professional consensus on what best supportive care for PPMS might be or how much it might cost. The concept of best supportive care is idealistic. It is unrealistic to assume that all people with MS have access to high quality care that fully meets their needs. The reality is that people with MS often have very limited access to services. It is clear from the data collected in our survey that people with PPMS have a high level of need for NHS care. Given the wide range of symptoms that people with PPMS may experience, it is important that there is access to a range of therapies delivered by skilled health professionals, competent in MS care. In reality, access to NHS and social care interventions such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. Calculation of the cost of providing best supportive care cannot assume an ideal situation where these services are readily available. We are aware that in some areas, people with PPMS have been effectively 'discharged' from MS services, either due to a perception that there is no treatment available for PPMS or due to limitation in service capacity. Overwhelmingly, the message that people receive from MS health professionals is that there is no treatment available for PPMS. The quality of and access to care is highly dependent on where an individual lives. An MS Society report found that 40 per cent of MS specialist centres failed to offer people with MS a truly multi-disciplinary clinic[6]. This was also reflected in the Royal College of Physicians national audit of services for people with MS which found only 43% of people said they knew they had access to specialist neuro rehabilitation and 57% said that they had access to specialist MS physiotherapists[7].

[5] Butzkeuven H, et al. EPR1087 Risk of becoming wheelchair-confined in patients with primary progressive multiple sclerosis: data from the ORATORIO trial and a long-term real-world cohort from MSBase Registry. Eur J Neurol 2018;25(Suppl 2):320.
[6] MS Society, MS 2015 Vision, (2011)
[7] RCP and MS Trust, National Audit of services for people with Multiple (2011)

	In 2011 the National Audit Office report for services for people with neurological conditions found that the case loads of MS nurses varied extensively in each Strategic Health Authority[8]. A more recent survey[9] conducted by the MS Trust in 2016 found that on average, people with progressive MS are seeing MS specialists much less often than people with relapsing MS. People with PPMS and their families go to great lengths to remain active and independent and do whatever they can to stay in work. This often involves paying privately for treatments with limited availability through the NHS, such as physiotherapy or chiropody, or treatments which are not available at all, such as Sativex and Fampyra. This further demonstrates that, on the ground, "best supportive care" does not meet the needs of people with PPMS. We do not believe that modelling accurately reflects the true experience of NHS treatment for many people with PPMS and that, for some people, progression is more rapid due to limited availability of care.
7	**Treatment waning** There is no clinical evidence for treatment waning. The manufacturer has been very clear that ocrelizumab causes negligible levels of neutralizing antibody and has reported a sustained treatment effect in an open-label extension of a relapsing-remitting MS trial. While we acknowledge that it is difficult to extrapolate from two year clinical trial data to long term treatment, we wish to emphasise that there is no clinical evidence to support loss of efficacy. The ACD states (3.11, p11) "The ERG included treatment waning in its base case, implementing it by reducing the treatment effect of ocrelizumab on slowing disease progression between EDSS states by 50% after 5 years. The committee concluded that "the company's assumption of no waning of treatment effect was too optimistic, but the ERG's approach may be too pessimistic. The true waning of treatment is likely to lie between these 2 approaches." This highlights the arbitrary nature of assuming treatment waning. The use of treatment waning in multiple sclerosis technology appraisals has become de facto, in the absence of clinical evidence or biological plausibility, the only purpose being to force an increase in the ICER. Further research is clearly needed to ensure an evidence-based approach to treatment waning.
8	**Conclusion** The MS Trust wishes to state in the strongest possible terms the potential benefits of ocrelizumab for PPMS in terms of meeting the huge unmet need, delaying disease progression, and the impact on the daily lives of this group of people. Although people do all that they can to minimise the impact PPMS has on their lives, they are all too aware that there is nothing that will slow down the progression of their disease. As well as the long-term impact on mobility, work and independence, the psychological impact of a future with PPMS should not be underestimated. Our research has highlighted that the message people received from MS health professionals is that there is no treatment available for PPMS, which adds to that burden. The introduction of disease modifying drugs for relapsing remitting MS has been the catalyst for significant improvements in MS services for people with relapsing MS. The introduction of a treatment for PPMS would similarly result in a greater focus on services for progressive MS and a

[8] National Audit Office. Services for people with neurological conditions (HC 1586). TSO, 2011
[9] MS Trust. Is MS care fair? MS Trust; 2016

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	more pro-active approach to managing PPMS which would ultimately benefit a much wider group of people with PPMS than just those who might be eligible for ocrelizumab. We are delighted that NICE recognises the innovative nature of ocrelizumab and urge NICE, NHS England, the Department of Health and the manufacturer to find a solution which enables those eligible to access this drug as soon as possible.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Association of British Neurologists**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are disappointed that Ocrelizumab will not be available at current cost. Ocrelizumab is the first licensed medicine for primary progressive multiple sclerosis and meets an unmet need. Slowing disability progression will have a noticeable effect on disability progression in upper limbs as well as walking. There will be reduced costs from need for Care, need for aids and benefits. More people may be able to stay in employment.
2	Although definitions of “early” and of “active “ disease on MRI pose problems with the increase need fro MRI and gadolinium use practical definitions and use of other sequences such as diffusion weighted change may mitigate this burden.
3	The risk of PML with Ocrelizumab is most likely to be similar to Ritixumab, Clifford et al Arch Neurol 68(9) 1156-1164 form 2011 reported only 4 cases in 129,000 people treated of Rheumatoid arthritis, estimating a risk of 1 in 25,000.
4	Facilities for administration and safety monitoring of Monoclonal antibodies already exist in MS centres due to use in relapsing disease, although increased need for MS Nurses, Infusion capacity and access to Neurology as well as MRI is to be anticipated.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise and all information submitted under ‘academic in confidence’ in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: ‘academic / commercial in confidence information removed’. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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unlawful or otherwise inappropriate.

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Name	Mrs Yvonne Pettigrew
Role	Patient Expert
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 2.0 **Page 4**	The market authorisation indication, considered by the ERG to be 'vague and subjective' has in my opinion created an avoidable lack of clarity in the understanding of "early primary progressive multiple sclerosis" in this context by defining this "in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity". Could consideration be given to changing this to "in terms of disease progression and level of disability" to be consistent with the ORATORIO trial? These two elements would enable: objective targeting of the eligible patient population; better definition of the start point; exclusion of the additional MRI costs.
Section 3.1.0 **Page 4**	It is correct, as stated, that there are currently no disease-modifying treatments approved for primary progressive multiple sclerosis (PPMS). However it is incorrect that "clinicians can only offer interventions designed to control symptoms", rather they "can only offer interventions to potentially manage symptoms" as without disease modification they cannot be controlled and will continue to progress. It is this aspect of the disease that is most terrifying for patients.
Section 3.3.0 **Pages 5-6**	Defining who will benefit from ocrelizumab may not need to increase demand for MRI scans. By its very nature PPMS features symptomatic deterioration and functional decline which evidences the ongoing inflammatory activity. The 2013 revised McDonald criteria incorporated categorisation of active or not (based on recent clinical relapse or MRI lesion activity) and progressive or not (based on clinical assessment of disability) according the disease course in a preceding time period e.g. 1 year. Would it therefore be reasonable to adopt the same criteria i.e. using clinical & functional systems assessment and the EDSS 3.0 - 6.5 as per the ORATORIO trial criteria to determine eligibility. (The former is necessary because at the lower / earlier grades of the EDSS, deterioration within sections may not effect a change in the score).
Section 3.5.0 **Pages 7 - 8**	The committee discussed the difficulties in defining "early" disease in NHS practice and concluded the EMA definition used

	for the marketing authorisation to be used. However, this brings with it the dependency on, and costs of, MRI scans. Would it be possible to review this decision and instead define 'early PPMS' in terms of confirmation of the early phase of deterioration using the "level of disability", 3.0 - 6.5 (to be consistent with the ORATORIO trial), and the confirmation of "disease progression" deterioration within previous time period e.g. 1 year (to be consistent with McDonald criteria)
Section 3.10.0 Pages 10 -11	Concerns raised about using data from the MSBase registry are understood. Can the committee make recommendation for a PPMS population long term follow-up registry to overcome this for future. Has the MS Register been considered ? 17048 people have joined the study so far with 29 participating MS Clinics. The EDSS is one of the 9 measures used.
Section 3.13.0 Pages 12 - 13	"What would an acceptable stopping rule be?" I suggest "when there has been no evidence of disease progression i.e. assessed symptom deterioration and /or EDSS score increase, during a preceding 12 month time period.
Section 3.19.0 Pages 16-17	Given that data from the ongoing trial is unlikely to address the uncertainties identified by the committee, specifically related to 'the extent of treatment waning and how long people would stay on treatment' I suggest it is essential the company to build this into future studies. In the interim is there a subset of the ORATORIO trial who continued to show disease progression that could illuminate understanding of when to stop treatment and the effect this may have on affordability?
General	Very disappointed that cost benefit cannot be demonstrated as ocrelizumab represents such a life-changing step change for patients with PPMS. Question: If 'early PPMS' could be more easily defined by "early phase of disability (EDSS 3.0 - 6.5) and active progression of symptoms within recent 12 month", and the end point of treatment be clarified as "when there has been evidence of further progression (using EDSS) whilst on treatment", could the MRI costs be excluded, and the time on treatment more accurately costed to potentially deliver an affordable model ?

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	PhD Scientist, lecturer
Organisation	
Location	Scotland
Conflict	None
Notes	
Comments on individual sections of the ACD:	
General	Ocrelizumab is thought now to possibly delay progression to wheelchair by up to 7 years in PPMS patients - this news from the 4th Congress of European Academy of Neurology following phase 3 trials after 24 months of data. Does NICE not recognize that no other treatment has been effective in PPMS except Ocrevus? And now to deny something that can have a very meaningful impact for 7 years in people with PPMS...shame on you. I don't have PPMS, I have RRMS, but this announcement made me cry for it shows the lack of care for the quality of life of people with chronic progressive diseases in this country. Also this seems economically shortsighted as the economic production from people with PPMS in the economy by working much longer could be alleviated. If someone can work 7 years longer, this should be taken into account into so-called "cost-benefit" analyses. https://multiplesclerosisnewstoday.com/2018/06/15/latest-ocrevus-data-in-ppms-at-ean-2018-meeting-announced-new-trials/

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	Not stated
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	You are discriminating against a whole group of PPMS people compared to RRMS because there is NO treatment (drug) available on the NHS to make a cost comparison to what a person with PPMS receives, ie, £0.00. My husband's sole treatment at the moment is a yearly appointment with his consultant and a physiotherapist. That's it! NICE can prevent his deterioration which WILL result in my husband being incapacitated. You have just destroyed the hopes of a whole group of sufferers, please reconsider your decision, if you prevent him now from deteriorating further, it will be a long term saving for the NHS and its future.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	This is the first ray of hope for us with PPMS. DMD are not working for me (diagnosed 2 years ago) so would urge you reconsider this.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	
Location	England
Conflict	None
Notes	I am a PPMS sufferer
Comments on individual sections of the ACD:	
General	Ocrelizumab has been rejected for PPMS sufferers. They say that we should just carry on with our current PPMS drugs. I am not aware of any other drugs for PPMS, so how can we carry on with it? Ocrelizumab was our first and only chance!

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	I am newly diagnosed with ppms and im scared my walking has already started to deteriorate please reconsider allowing ocrevus so I can have a small quality of life as opposed to none. Please please reconsider your decision

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
General	I was diagnosed with Primary progressive MS in 2010 and my condition is gradually worsening as time goes by. Ocrelizumab has been approved by NICE for use on the NHS for relapsing remitting multiple sclerosis whereas there are lots

	of available treatments for this type of MS at the moment. Clinical trial results show that ocrelizumab slows disability progression in Primary progressive as well as relapsing remitting MS. Ocrelizumab is the ONE AND ONLY option for a slower disability progression for people in the Primary progressive MS population. The slower disability progression is the reason that ocrelizumab has been approved for relapsing remitting MS so why cannot it be approved for Primary progressive MS. I believe that people with Primary progressive MS in general are being discriminated against by not having Ocrelizumab made available to them on the NHS, because it is the only approved disease-modifying treatment for use in Primary progressive multiple sclerosis.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	As a recently diagnosed sufferer of PPMS I am very disappointed at this decision from NICE. With no NHS drugs, treatment or support offered except the services of a consultant and an MS nurse once a year it would be good to have the opportunity to take a drug which has been proven to delay progress of the disease. I understand the drug is expensive but it may well delay the time when I need various aids around the house and a wheelchair, all of which cost the NHS. At the moment I am funding my own physiotherapy because there is none available in my area on the NHS. I may well not always be able to afford this.

Name	[redacted]
Role	Public
Other role	Engineer
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	So very disappointed with outcome of ocrelizumab for rejection for ppms,lived with this for past 8 years with no hope, this was my only hope

	So disappointed on rejection of ocreizumab for ppms. it was my only hope

Name	[redacted]
Role	Carer
Other role	Retired civil servant
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	Please please re-consider Ocrelizumab for Primary Progressive patients as my partner suffers from this awful illness for which there is no treatment. He has tried steriods and other medications to no avail. We were waiting with bated breath for this drug to be released, to halt his progression, and are devastated to find it is not being allowed. I have followed Ocrelizumab User Groups on web-sites on FB and they have had great results in America and Europe. Even if we could pay some money towards getting it, if you would only release it. Relapsing Remitting patients have many other drugs to use and experience relapses, while my partner suffers every day and worsens every day. Please re-consider releasing this drug to a group of people who have nothing to live for. Many thanks.

Name	[redacted]
Role	Patient
Other role	Lunchtime supervisor
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I feel very disappointed in this decision. There are no other treatment options for me as a sufferer of ppms. The only treatment I have ever been offered is alleviation of symptoms in the hope that something will come along to help in the future. Ocrevus was a potential "help in the future". Without this, all I face is a worsening of my condition being "managed".

Name	[redacted]
Role	Patient
Other role	Software engineer
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	My name is [redacted] and I am 59 years of age. I live in [redacted] and work as a professional engineer in [redacted].

	In 2006, I was diagnosed with Primary Progressive Multiple Sclerosis (MS) which came as a major blow. Over the years, I have witnessed my walking steadily worsen. As a result, I now walk with a single stick. At night, I experience strong spasms which interrupt my sleep and interfere with my quality of life. When out and about, I have to be extremely careful to not trip and fall over which has happened a number of times over the years. My reduced mobility limits what I can do on a daily basis; trips out have to be planned for like a military campaign. I worry about the future and what that will bring for me. It's hard for my wife [redacted] who supports me as much as possible, says nothing but I know that she worries too. When Ocrevus (Ocrelizumab) was initially announced by Roche in 2015 as a major game changer for MS, and in particular Primary Progressive MS, it filled me with huge and excitement and hope for the future. I have tracked it's progress with great interest. I was so pleased to read that it has been recently approved by NICE for use by the NHS for Relapsing Remitting MS; I believed it was only a formality that it would be approved for Primary Progressive MS within the next few months. I was totally devastated to learn from an MS Trust newsletter in the last few days that NICE have rejected it's use for Primary Progressive MS by the NHS. This piece of news completely extinguished my single source of hope for the future in altering the course of deterioration caused by this awful condition. I would like to appeal to NICE to please reconsider their decision for my sake and the thousands of others in the UK affected by Primary Progressive MS.

Name	[redacted]
Role	Patient
Other role	Retired due to MS
Organisation	
Location	England
Conflict	No
Notes	I'm currently taking Fampyra and self funding this is becoming impossible as £186 every four weeks is a lot of money when you don't work!
Comments on individual sections of the ACD:	
General	Ocrelizumab please help us patients with PPMS there are no medications out there for us at all. Our consultants have been telling us great things about this drug. Just give us the opportunity to try. RRMS have so many choices give us a break!

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	See emailed comments to [redacted] MP. Dear [redacted] You helped us in our fight to get [redacted]'s PIP reinstated. The following points highlight a continued lack of help and support from our healthcare system. 1. We were forced in to a prolonged and degrading battle with the DWP and Capita to get [redacted]'s PIP reinstated. 2. There is no longer a specialist MS consultant at Leicester General hospital, [redacted]'s last two appointments have both been cancelled and she has not seen an MS specialist in over a year with no prospect of seeing one at all in 2018. 3. NICE have decided not to approve Ocrelizumab for use on the NHS despite it being the first and only disease modifying drug currently available anywhere in the world for the treatment of primary progressive Multiple sclerosis - PPMS. NICE acknowledge the effectiveness of Ocrelizumab in slowing down the disease but say it does not represent value for money compared to other routine PPMS treatments available on the NHS, these so called treatments only treat the symptoms not the cause, in [redacted]'s case anti depressants, anti spasm and neural pain control drugs that have little to no effect and do not slow the progression of her disability which is not cost effective when you consider she is likely to be more of a burden on the NHS sooner and longer without the benefits of Ocrelizumab. NICE have approved it for the treatment of relapsing MS but this makes no sense, it would have been more plausible to approve it for PPMS only on the grounds of cost and the numerous disease modifying drugs already available on the NHS for the relapsing type. Our hopes and the hopes of many other PPMS sufferers were pinned on this new drug, we now have no hope. We contribute our hard earned tax pounds to the state but when we need help we are forced to beg for it, this is a sad and shameful indictment of the country we live in. I would be grateful for any assistance you can once again provide in highlighting these issues to your government colleagues in Parliament. I will be taking our plight back to the press.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	In your Initial response for use with PPMS you mention "routine treatments", what do you mean asI was told my neurologist that nothing was yet available.

Name	[redacted]
Role	Patient
Other role	Graduate
Organisation	
Location	Europe
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I'm an italian patient with Primary Progressive Sclerosis. For us multiple sclerosis advances quickly and ocrelizumab can help us to feel a little better. Ocrelizumab is available on WEB but the cost, over 8.000 USD each, (3 infusions are needed in 6 months, so are over 24.000 USD), is not suistanable for those who are no rich. Please, please, please, do not cancel the hope for a less dark future. British are a great people and the gratness is measured by the support of those in need of help.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Approval should be given for use of ocrelizumab for PPMS if recommended by the attending consultant. Manufacturer funded trials should be permitted. Cost savings to the NHS need to be emphasised as any improvement in PPMS suffers health will be less draining on the NHS The drug should be available to all MS sufferers for whom the drug was intended for,

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I have been diagnosed with secondary progressive multiple sclerosis in march,2017.I had to take early retirement at the age of 58 because I couldn't work anymore. There is no treatment for me out there and I saw my consultant 2 weeks ago and gave me some hope when he talked about this new drug and that he said he hoped that it would be suitable for me. But with Nice saying no to this drug all hope has now gone that it might be suitable for me with secondary progressive multiple sclerosis.I am getting worse each year and you have just dashed all my hopes.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Wales
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	I would like NICE to reconsider their recent decision regarding Ocrelizumab for sufferers of PPMS. Since my diagnosis in 2015 I have felt totally isolated with nothing on the horizon in terms of medication for this dreadful condition. I've spent most of my working life helping others and have never asked for anything in return. The approval of Ocrelizumab would at the very least have given me and MANY others a glimmer of hope in an otherwise dark abyss. I would respectfully ask you to reconsider your decision thus giving many of us something positive to look forward to as we have precious little thus far. Kind regards

Name	[redacted]
Role	Patient
Other role	Childminder
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Hello,

	As a PPMS sufferer I am deeply, deeply saddened to hear the initial result regarding Ocrevus. It is unfair to be have been diagnosed with MS in the first instance as a 42 year old, previously very active mum of two. To then be told there are no possible drugs available to potentially help with my condition was heartbreaking. The only glimmer of hope on the horizon was the potential availability of Ocrevus. It is very hard to cope on a day to day basis and having to explain the situation to my two boys was indescribably difficult. To then have my only chance of improvement taken away because of what type of MS I have? Ludicrously unfair. I feel discriminated against through absolutely no fault of my own. I anxiously wait further comment on this consultation.

Name	[redacted]
Role	Patient
Other role	Senior Systems Analyst
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	I am extremely saddened to hear this news today. I am 38 years old, and I have SPMS. I was diagnosed with RRMS, in 2009, and went onto Rebif for a few years, and then Fingolimod, until 2017. I try to be proactive, and try to stay positive for the future, but with there being no medication for SPMS, this is incredibly challenging. As is life in general when living with this disease. News of Ocrevus being made available gave me some hope for the future. Now once again, my hopes have been crushed, and future life uncertain. I urge you to please overturn your decision, and give MS sufferers some hope!!!

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS?

	NICE's decision is both upsetting and extremely concerning.

(Note, 8 people have submitted the same comment)

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	'Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both upsetting and extremely concerning.'

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Ocrevus is the ONLY approved, effective treatment in the world for PPMS. In not approving it for this condition it discriminates against and actively disadvantages sufferers of PPMS solely on the grounds of the type of condition they have. It is puzzling that others suffering from a different variant of MS have had the treatment approved. Why are people with PPMS being treated less fairly than those with RRMS? The decision of NICE is both upsetting and extremely concerning.

Name	[redacted]
Role	Public
Other role	Sales Director
Organisation	
Location	England
Conflict	No

Notes	
Comments on individual sections of the ACD:	
General	Why are people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both confusing and extremely upsetting to those entire families having to live with this debilitating affliction.

Name	[redacted]
Role	Director
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both upsetting and extremely concerning!

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Ocrevus is, I believe, the only approved, effective treatment in the world for PPMS. To not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Grateful if you would explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both very upsetting and extremely concerning.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	'Ocrevus being THE ONLY approved, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? NICE's decision is both upsetting and extremely concerning.'

Name	[redacted]
Role	
Other role	Retired Senior Social Worker Local Authority/NHS/ British Red Cross
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Two close members of my family had and have PPMS. During my professional career I came in contact with many others. I observed with dismay and sadness the detrimental effects this has on the lives of these sufferers. It is unjustifiable and inhumane to deprive PPMS patients of Ocrelizumab on any grounds whatsoever this being the only approved, effective treatment in the world for those with this diagnoses. To exempt the PPMS patients from the benefits while at the same time allowing the the treatment for RRMS patients is discriminatory and unacceptable. This is simply unequivocal. How many more sufferers need to experience these or similar events in order to attempt to save expense within the NHS? If it is the object of NICE to serve the benefit and protect NHS patients, surely it is also to provide the proven drugs and the methods available to facilitate this.

Name	[redacted]
Role	Public
Other role	Company Director
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	

General	It seems to me that failure to provide this treatment discriminates against PPMS sufferers as approved treatments are available for RRMS.

Name	[redacted]
Role	Family
Other role	Account Director
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	It's appalling that even though this has such substantial benefits to those effected the government is proving to be the obstacle in providing this life saving remedy

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	This is a very disappointing decision and one that I hope will be reversed at a later date. There are currently no treatments of this kind available for PPMS and people suffering should be given access to Ocrelizumab to improve their quality of life.

Name	[redacted]
Role	Patient
Other role	Pet sitter and dog walker
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Hi, I have been diagnosed for the last ten years with PPMS. Things have changed and developed over the years and I now use an FES to help me walk. Other than that I take no medication for my condition. I had heard about the news of a new drug; Ocrelizumab that was going to help people like me with PPMS by halting the development of MS. I hear that it's going to be rejected now for people with the same condition as me but will now be used for RRMS patients. This really worries and upsets me as there is so very little out there to help me and I just feel like we've been hung out to dry, while the RRMS people have no end of

	treatments and medications at their disposal. I know both versions of MS are horrible but I feel like as the MS takes a stronger hold I'm running out of time! I just hope you might be able to reverse the decision and make it available to me and others? Many thanks

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	The wife of a good friend suffers from this and I am told that Ocrevus is the proven, effective treatment in the world for PPM. Consequently, not to approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. This does not seem fair to me.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I was diagnosed with Primary Progressive MS about 2 years ago. I was determined to deal with this positively and have moved to a bungalow and have continued to stay as healthy as possible by taking regular exercise and eating properly. However my symptoms are increasing. I was devastated to read that NICE have removed the possibility of slowing down the progression of this disease and that I am likely to become less independent and a burden on the state more quickly than necessary. I feel that MS is a poor relation compared with other conditions and I hope very much that NICE will reconsider its decision in order to give MS sufferers such as myself some hope of delaying the disease.

Name	[redacted]
Role	Public
Other role	Customer service director
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	'Ocrevus being THE ONLY proven, effective treatment in the world for PPMS - to not approve it is discriminatory against people suffering with PPMS on grounds of the type of condition they have, as others with a different variant have had the treatment approved. Please explain why people with PPMS are being treated less favourably than those with RRMS? And how you can defend the reasoning in offering to one variant and not the other?

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Why are you discriminating against those who suffer with PPMS when other types of condition such as RRMS receive their treatment? Quality of life and live itself are at serve risk because of this.

Name	[redacted]
Role	Patient
Other role	Ill health retired
Organisation	
Location	England
Conflict	No
Notes	Just that I fully support the comments made by The MS Trust who on a daily basis know exactly the effects of having MS.
Comments on individual sections of the ACD:	
General	In no certain order : There is no treatment for PPMS, any drug that can have the potential to prevent/minimize further disability will be cheaper to the NHS/Govt as a whole than the costs to the country as a whole of increasing disability. The costs of numerous GP appointments, MS Nurses, hospital appts hospital admissions , including social care input from home carers to nursing care. The cost of people being unable to work & be retired due to ill-health, so cannot contribute to society but become a "financial burden" relying also on benefits. There is also the great

	personal impact not just for the person with PPMS but also the strain on family, friends and the community at large. People should be given the opportunity via their Neurologists to try the drug, if it shows no improvement for the individual then it can be stopped, but not to allow someone the opportunity to try it is cruel.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I have had Primary Progressive MS for past 20 years and have not received any medication to relieve my symptoms Ocrelizumab is the first drug that shows any promise of slowing down the progression of the disease and I urge NICE to reconsider their decision.

Name	[redacted]
Role	Public
Other role	Engineer
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	An extremely disappointing initial decision on this very promising treatment. Please reconsider the millions of people that are suffering as a result of MS.

Name	[redacted]
Role	Patient
Other role	Senior Manager for Accountability (Education)
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	My sister (PPMS) and I (RRMS) were both diagnosed with MS in 2016 and 2017. Almost immediately I was prescribed my DMT of choice, Tecfidera. My sister was advised that, should Ocrevus be approved for UK use, she would be a strong candidate in terms of criteria.

	I am not medically trained and therefore not able to contribute in terms of technical details. However, I strongly object to the NICE decision to deny approval for a UK licence for patients with PPMS on the following grounds: 1.2 'Costs are much higher than those NICE normally considers an acceptable use of NHS resources' Given that the NHS is currently finding the cost of my prescription for Tecfidera as acceptable (approximately £17,000-£20,000 per annum) the figures cited on the consultation document for Ocrevus do not appear remarkably dissimilar and one would question why Ocrevus for RRMS patients is not objectionable to the NHS. There is nothing 'normal' about MS; the NICE response to the drug being ethically and medically acceptable cost-wise for RRMS patients and not PPMS patients is discriminatory on grounds of condition-type, for which the boundaries and definitions are case-by-case, often the subject of uncertainty. You allude to this in Section 3.3 of the consultation document. 3.3 Likely to increase demand for MRIs This would need to be clarified as to whether the objection is regarding the cost of MRIs to the UK on an annual basis, or whether there is an agreed and set limit per patient of entitlement to MRIs which, I do not believe there is. I have been able to obtain and MRI on request and was never made aware by the NHS that I would be resticted on future MRIs to monitor my treatment efficacy and condition. There are many factors inherent in the UKs ageing popiuation which may, or may not warrant an increase in demand for MRIs. This is to be anticipated within any country with an increasing age-expectancy. Again, it is discriminatory to suggest that PPMS patients are less-entitled to a possible increase in their MRIs and should therefore not be described an effective DMD. The reduction in the use of gadilinium over time due to concerns over long-term safety is a recommendation which extends beyond the confines of MS; therefore this is not a consideration which should be a factor in declining approval for Ocrevus. Risks are always associated with operations, procedures and medications; this is why patients sign consent forms. 3.11 The company assumed that [efficacy] did not waiver over time. As a non-specialist, I would argue that there is no guarantee for any DMD on its projected efficacy over time. If there were, there would be no degeneration or worsening of symptoms with any variant of this, and other conditions. And on that basis, the NHS continues to prescribe me Tecfidera at great cost to the NHS. To deny approval for funding Ocrevus to treat PPMS makes no medical or ethical sense, given the arguments against approval.

	This medication has shone the single light of hope on the horizon for patients with PPMS for the first time; to deny patients the right of access which Europe, the United States and Canada has provided its citizens makes no sense based on the objections raised by this document. It discriminates against patients based on the type or variant of the same disease when clarity of definition is often questionable. It assumes that the burden of cost for increased MRIs and Ocrevus prescription will be greater than the cost of longer-term care and other NHS resources, an assertion which is impossible to predict. NICE initially made similar objections to the prescription of Ocrevus for RRMS in 2018 which it has now overturned, given that Ocrevus has now been approved for UK use with RRMS patients. It is with my great hope and anticipation ,that NICE will make the same decision with Ocrevus for the treatment of UK patients with PPMS.

Name	[redacted]
Role	
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I urge you to reconsider your decision on Ocrelizumab as a treatment for PPMS . There are currently no treatments available , this puts people with a diagnosis of PPMS at a distinct disadvantage . My husband was diagnosed in 2006 . I have watched his mobility decrease steadily in the intervening years . He can only walk short distances with a stick and requires the use of a wheelchair for longer distances. Trips out have to be planned meticulously in advance as he is unable to use public transport. He has remained positive despite a significant decline in his independence & a curtailment of his hobbies & interests (playing music, photography) He has been proactive in the management of his condition and is vigilant about doing his home exercise programme. He also swims up to 3 times a week . He subscribes to the MS trust newsletter & has remained optimistic that there will be a treatment available soon for PPMS . Please give hope to my husband, myself & all the other people with PPMS by reversing your decision on Ocrelizumab

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Wales
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Given the limited range of treatments available for PPMS the argument of not offering value for money I find abhorrent. I really could not care what the treatment costs when non-vital cosmetic surgery and IVF is offered on the NHS. The issue surrounding approving a drug for use should be around risk to the patient which ultimately is up to the patient anyway. So approve the medication and leave the application of the medication up to the neurologist and the patient.

Name	[redacted]
Role	Patient
Other role	IT Consultant
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I'm a suffer of PPMS. Ocrelizumab has been approved for treatment of RRMS. I believe the decision not to approve ocrelizumab for treatment PPMS is wrong for the following reasons. 1. Whilst there are multiple DMTs for RRMS, there are currently none licensed for PPMS. 2. There are fewer suffers of PPMS that RRMS. I understand that only 14% or so of MS suffers have PPMS. The cost for the NHS therefore would be significantly less than approving it for RRMS.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	There are no other treatments available for PPMS.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	I was diagnosed with PPMS in October 2014. My mobility and quality of life is deteriorating much faster than I had anticipated. I have had to finish work a job and people I loved. Tasks I can carry out are becoming fewer. Ocrelizumab gave me some hope. Maybe the progression of my disease could be slowed down. I spoke to my consultant who said I would be suitable and in fact ideal for treatment with Ocrelizumab. I waited for Ocrelizumab to get a European licence for RRMS and PPMS. I saw NICE reject and then approve Ocrelizumab for RRMS. I waited for the NICE decision on PPMS. This is the first disease modifying drug for PPMS and so I was confident it would be approved. To say I was disappointed when NICE rejected Ocrelizumab for treatment for PPMS is an understatement. My lifeline was gone. I hope that NICE will reconsider and approve Ocrelizumab for PPMS. I know there is a cost factor and NICE consider treatment not to represent value for money to the NHS but for me and others with PPMS this is the only treatment that will slow down the progression of the disease. The only routine NHS treatment is symptom management, prevention of complications and health and wellbeing. People with PPMS need a treatment that will slow down the progression of their disease. Ocrelizumab is that treatment. I hope NICE will reconsider and approve Ocrelizumab as an NHS treatment for early PPMS.

Name	[redacted]
Role	Carer
Other role	Cabin crew
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	You've stated that there is no current treatment for Primary Progressive MS. My mother has this type of MS and it is heart breaking to see her deteriorating every day. This drug was a glimmer of hope for her. You've recognised that this drug can help with PPMS. A lot of people had hope resting on this drug being passed and it's soul crushing to see that it has been rejected because of cost. What is the cost of human life? There are treatments for other kinds of MS but not PPMS. Not everybody can afford to pay the extortionate fees that are associated if trying to get this drug privately. I really do hope that you reconsider your decision, without this drug I'm sure that my mother and many other people who are living with PPMS

	will continue to deteriorate.

Name	[redacted]
Role	
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Yes have PPMS -I am dumbfounded that the decision has been made not to approve the first ever drug with a licence for PPMS-I have recently had to give up work due to my condition and that means I pay less tax and may have to claim benefits. This does not make financial sense to take people out of employment when you have the ability to improve their lives. To licence for RRMS when there is a huge amount of choice of treatment seems senseless. Of course, I understand the cost implications but I currently I have no treatment so any cost will compare badly to that of current (no!) treatment. Also, pharmaceutical companies will stop developing drugs to help people like me if they are not used.

Name	[redacted]
Role	Carer
Other role	Teacher of Law
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Being the carer of someone with PPMS, I was disappointed with the recent decision not to allow the use of ocrelizumab for patients with this type of MS, particularly as I have taken note of its progression through Europe and its acceptance for Relapsing Remitting MS. More so, it is even more disappointing inasmuch that ocrelizumab is the only "real treatment" available for PPMS, which can actually slow down the progression of the disease, as all other things/drugs, called treatments, which have been made available so far, only actually deal with "symptom management" of PPMS. As ocrelizumab is the only drug available to have any chance of slowing down PPMS, you would think that this drug would have been made a "priority" for those with PPMS, rather than those with RRMS, as patients with RRMS have many more drugs available to help them live and cope with their disease and without this treatment PPMS patients will undoubtedly develop into serious disability, in the majority of cases. Having a Law degree, I also believe to allow ocrelizumab for one type of MS and not the other type is discriminatory, inasmuch as those with PPMS have no real treatments available to slow down their

	disability progression, whereas those with RRMS seem to have lots of treatments available. As a carer of someone who is on the Expanded Disability Scale, already scoring 6.0, having only been diagnosed with PPMS three years ago, the only way forward which I can see without ocrelizumab is one of my partner suffering from severe disability, a way which would be at least slowed down if ocrelizumab had been passed for PPMS. Though there is obviously a cost factor which NICE has to consider, the cost in real terms of PPMS cannot be under-estimated for patients with the disease. I am watching as my partner is deteriorating and knowing that there is a treatment now available which NICE have refused for PPMS is frustrating, gutting and unfair. As you read this I hope that someone close to you does not have to suffer from this debilitating condition and you do not have to watch them deteriorate as quickly as I have. Ocrelizumab has offered hope to patients with PPMS, hope that until now patients have not even been able to consider; I hope that after consultation NICE will pass ocrelizumab as the benefit in real terms for patients with PPMS is life-changing, a benefit which certainly outweighs the cost.

Name	[redacted]
Role	Patient
Other role	Business coach
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
General	Focus must shift from a pure financial consideration to the quality of life for PPMS patients. They need hope and ocrelizumab provides that and encourages further work overall to find a remyelination solution. If cost benefit is the deciding factor please consider the cost to the NHS of mobility equipment, physio and hospital spaces long term. Ask for patient contribution towards cost of treatment if you want to test patient needs.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	For 20 years I have had chronic/ relapsing MS.I cannot begin to describe this living nightmare. Please give these people hope for life.

Name	[redacted]
Role	Carer
Other role	Retired physiotherapist
Organisation	
Location	
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
General	My 32 year old daughter was eventually diagnosed in 2016 with PPMS and was told by a neurologist that he had no treatment to offer her. To be told you have an incurable life changing progressive disease is a shattering experience and now that there is a drug that gives some hope to people with PPMS the NHS needs to be able to offer this. Without any treatment people with this disease will deteriorate and become a massive burden to health and social services in the future. It must be more cost effective to offer a drug which has a chance of delaying the progression of disability than to offer nothing. My daughter has embraced diet, lifestyle and exercise but we are realistic that these only help to a degree. My daughter and others like her desperately need to be offered this drug so they have some hope for a future.

Name	[redacted]
Role	[redacted]
Other role	
Organisation	MS International Federation
Location	
Conflict	I have no personal pecuniary interests to declare relating to the pharmaceutical industry. MSIF does receive financial support from a number of pharmaceutical companies, but no company has had knowledge of or influence over this letter. Neither myself nor MSIF receive money from the tobacco industry
Notes	
Comments on individual sections of the ACD:	
General	Thank you for the opportunity to comment on your interim decision regarding the use of ocrelizumab for the treatment of primary progressive multiple sclerosis. The MS International Federation (MSIF) is the world's only global network of MS organisations. The movement is made up of 49 MS organisations, with links to many others around the world. MSIF and its members campaign for increased awareness of the disease, support scientific developments and work to improve access to treatments and healthcare. Through capacity building, information and resources, MSIF supports and collaborates with organisations in countries where there is limited provision for people with MS. The global MSIF movement works together to improve the quality of life of

	everybody affected by MS. You will be well aware that technology appraisal determinations by NICE not only have great impact on the use of treatments in the UK, but carry great weight around the world, with many countries using NICE judgments at least as part of their own determinations on what treatments should be covered for reimbursement. Hence MSIF is interested in your decision on ocrelizumab not only for people with MS living in the UK, but around the world. **Unmet Need** There was great excitement around the world when the trial results for ocrelizumab were published. People with primary progressive MS (PPMS) at last had hope that their debilitating disease could at least be slowed and their quality of life preserved. Then came better understanding of the probable significance that there was a sub-group of people with radiological evidence of inflammation who responded particularly well to treatment and on that basis the marketing authorisation was granted only for that sub-group. That of course left many people with PPMS disappointed, but on the other hand targets ocrelizumab where it can do most good. We hope that, after considering the feedback of stakeholders you will reach a revised decision so that people with PPMS, where there is also evidence (through MRI) of features characteristic of inflammatory activity can access ocrelizumab through the NHS. The number of people who could benefit (in the UK) is not large in number, but this is the only currently licensed therapy that can slow or stop their disease. **Treating inflammatory damage and optimising medicines** Critical to the appraisal of ocrelizumab is an understanding of the primary disease mechanism being treated – auto-immune mediated inflammatory damage. Your appraisal accepts that ocrelizumab would be targeted at the sub group of people with PPMS with inflammatory damage, in line with the marketing authorisation. This is a real attempt at medicines optimisation, using the trial evidence to target the people who could benefit most. That is good for the people being treated, good for stretched healthcare services and good for taxpayers. Companies should be encouraged to break trial data down in this way. With the sub-population in mind, it is important when considering what constitutes the comparator of best supportive care to understand that the management of PPMS with evidence of inflammatory damage should not be regarded as being the same as the general PPMS population. Healthcare beyond pharmaceuticals should of course also be optimised. This is important as your interim appraisal seemed to put some weight on the argument that the NHS would face increased cost from a treatment regime for this population, not only through the drug costs, but through an increase in MRI scanning. The point being that people with PPMS were not thought to currently warrant regular MRI scans. However, for the sub-group of

	people whose inflammatory damage can be investigated, regular MRI should be considered best supportive care, especially as the imaging evidence can now make a difference to clinical management. Progress in imaging technology that enables the segmentation of a patient population, to better target treatment, should be embraced by NICE and medical practice generally. Therefore, for this sub population, MRI scans should not be considered an additional cost burden, but good practice disease monitoring. **Outcome Measures and Quality of Life** There is broad agreement that outcome measures for the treatment of MS need to be improved to better capture the heterogeneity of how the disease affects people and how those affects change over time. Innovation in this area should therefore be welcomed. For this appraisal there is the added impetus for innovation that the traditional focus (in MS treatment trials and consequent appraisals) on incidence of clinically significant relapses (a surrogate for disease activity) are not appropriate. For this appraisal, measures of various aspects of physical and emotional disability and impairments would inevitably need to be different to older RRMS submissions. Going beyond EDSS is a very positive step for the assessment of MS treatments. EDSS puts great weight on walking ability, which is certainly important, but underestimates other symptoms and functions. We were surprised therefore to see the interim appraisal rejected the added weight given in the ocrelizumab application to fatigue and upper limb function. In the case of fatigue, this consistently comes out as one of the most significant symptoms for people with MS. Hence the James Lind Alliance Priority Setting Partnership rated it as the most important symptom in their exercise to establish research priorities for MS. Fatigue also featured prominently in a similar exercise run by MS Research Australia. It was the most prevalent symptom in the MS in America Survey. And it was the top symptom in an American iConquerMS study looking at the key quality of life factors for people with progressive MS. Upper limb function is harder to evidence in this way, though mobility generally also features very highly in the exercises and studies described above. Then we should consider the question of how people with MS adapt to specific impairments, or don't. It is well known that people can adapt to disability and live higher quality lives than healthy people believe is the case. It is equally clear that some impairments (and symptoms) are harder to adapt to. Limited upper limb mobility is certainly extremely challenging, with impacts on every area of life and notably on self-care. Independence and the ability for self-care is hugely important to quality of life in people with MS, with obvious consequences for mental health too. Furthermore, the self-care aspect in this context has the added importance of being a key factor in driving up personal care costs. So when reconsidering this appraisal we hope that the

	Committee will reconsider the weight given to fatigue and upper limb function in the ocrelizumab application. **Summary** Ocrelizumab is an effective treatment for auto-immune mediated inflammatory damage. As well as having proven efficacy in relapsing forms of MS, it is a breakthrough product in also having proven efficacy at least for a segment of the primary progressive MS population. We hope that NICE will reconsider the aspects of the appraisal covered above and come to the conclusion that the treatment offers a hope for people with PPMS, but is also a good deal for the National Health Service and for taxpayers. We also hope that other appraisal authorities around the world take note of the special factors in this case and make ocrelizumab available, in a targeted way, through systems of reimbursement.

Appendix

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Figures

Latest data cut from open label extension (OLE) data

Roche would like to make the committee aware of new data supporting the long term efficacy of ocrelizumab in PPMS, which provides additional evidence of the treatment effect size as well as duration. Patients completing the phase III ORATORIO study could enter an open-label extension (OLE) period following unblinding of study centres, which started when the study was ascertained to be positive (initiated 12th Oct 2015). Upon completion of the ORATORIO double-blind placebo-controlled period, patients remained blinded and on-treatment as originally assigned for an additional extended controlled treatment period (ECP) ranging from the clinical cut-off date (24th July 2015) until the first dose of the OLE, and was completed when the last patient entered the OLE (27th April 2016). The most recent data cut off from the OLE extends to Week 336 (5th February 2018) (i.e. nearly 6 ½ years of follow-up).

Upon entering the OLE, patients previously receiving placebo switched onto ocrelizumab. To estimate comparative long-term treatment effect versus placebo during the OLE, crossover was adjusted using the Rank Preserving Structural Failure Time (RPSFT) model. This methodology is endorsed by the NICE DSU document TSD16 (1) and has been employed in many previous oncology NICE appraisals as well as a recent RRMS appraisal (2) to estimate treatment effect during OLE periods. RPSFT produces a counterfactual data set, adjusting the survival estimate in the presence of treatment switching in order to provide an estimate of the survival times that would have been observed in the absence of switching.

This type of crossover adjustment method assumes a common treatment effect, whereby the treatment effect received by those switching from placebo to ocrelizumab is assumed to be the same as the treatment effect received by those initially randomised to ocrelizumab. Clinical advice was sought at a recent advisory board organised by Roche to assess the validity of this assumption. Clinical experts considered this assumption to be valid as switching upon entering the OLE was not dependent on progression and hence the risk of progression can be considered equal between time of randomisation and time of entering OLE /switching. An alternative method of crossover adjustment, inverse probability of censoring weighted (IPCW) necessitates the use of longitudinal data on covariates and patient characteristics which predict treatment switching and prognosis. This information was not collected in ORATORIO OLE and therefore an IPCW model cannot be applied to the dataset to adjust for crossover. For the above reasons we therefore believe the RPSFT

crossover adjustment is a valid method to estimate the long-term treatment effect of ocrelizumab.

The robustness of the crossover adjustment was assessed in sensitivity analysis and the consistency of OLE results was assessed by comparing results across different disability outcomes (CDP-24, CDP-12 and 9-HPT).

The risk of selection bias was considered minimal in the OLE study. As numbers of patients from the MRI active cohort entering the OLE were too small to make meaningful conclusions, we analysed the numbers entering the OLE from the ITT population; very few patients chose not to enter the OLE study ([redacted]). The most common reason recorded for not entering the OLE was 'completed study' ([redacted]). In addition, the reasons for discontinuation remained consistent over the duration of the OLE. Many patients still remained on treatment without an event at the time of the latest OLE datacut (Feb 2018) and were administratively censored.

New evidence from OLE study in MRI active population

Treatment with ocrelizumab resulted in a [redacted] reduction in the risk of CDP-24 in the ocrelizumab group compared with the placebo-ocrelizumab switch group [redacted]) (Figure 1, Figure 2, Table 1, and

Table 2). When adjusting for crossover using RPSFT, treatment with ocrelizumab resulted in a [redacted] reduction in the risk of CDP-24 in the ocrelizumab group compared with “placebo” group ([redacted]).

These analyses indicate that the treatment effect size for ocrelizumab further after the first 3 years of treatment, from a 29% reduction in risk of CDP-24 in double (DB) period (company submission) to a [redacted] risk reduction in crossover-adjusted of DB and OLE period (Figure 1, Figure 2, Table 1, and

Table 2).

The increase in risk reduction of CDP over time is confirmed by analysis of results of CDP-12 (Table 3, Figure 3, and Figure 4). The size of treatment effect on upper limb function remains largely stable over time (HR 0.52 in MRI active population during period compared with [redacted] over DB and OLE period, adjusted for crossover using RPSFT) (

Figure 5, Figure 6, and Table 4).

Sensitivity analyses were performed as suggested by NICE DSU document TSD16 (1). An on-treatment model resulted in negligible difference. To explore the impact of the common treatment effect assumption, the treatment effect of ocrelizumab in the placebo arm was varied by -50% and -20% relative to the effect in the ocrelizumab arm. Results were relatively stable to this variation. Finally, the impact of re-censoring was explored as suggested in Latimer et al. 2018 (3) and showed only a small difference. In conclusion, the sensitivity analyses indicate that the crossover-adjusted effect size is robust to different analysis methods and assumptions (

Table 5).

The phenomenon of a lag time before reaching maximal treatment effect size on disability outcome measures has been observed in other trials of anti-inflammatory DMTs in progressive forms of MS (4). A biological mechanism has been proposed to explain the observed therapeutic lag of effect on disability accumulation with anti-inflammatory therapies, such as ocrelizumab, in progressive forms of MS.

This lag may be explained by the delayed neurodegeneration induced by prior inflammation and can be compounded where there is limited neuronal reserve left to compensate for this damage (5). The low neuronal reserve for lower extremity function may lead to a long delay between anti-inflammatory intervention and therapeutic benefit on EDSS progression. Therefore, it may take several years for the effect of an anti-inflammatory DMT on lower limb disability to become clinically apparent. The increased treatment effect size for ocrelizumab with regards to CDP-24 and CDP-12 appears to follow the pattern predicted by this hypothesis (Table 1).

Furthermore, as upper limbs are typically affected at a later stage of the disease than lower limbs (proposed to be explained by the decreased likelihood of a lesion in shorter length central axons projecting towards the upper limbs vs. lower limbs – known as the length-dependent MS axonopathy hypothesis, as well as the observation that the region of the spinal cord most commonly damaged is below that which serves the upper limbs), it is anticipated that they will have accrued less damage and retain higher reserve capacity. Therefore, not only is the subsequent clinically apparent disability less significant but also the retained reserve can compensate for any damage that does occur (5-9). Consistent with this, the maximum treatment effect of ocrelizumab on upper limb function is achieved after a shorter period of time i.e. without a significant lag, as more of the effect is acting on current or recent inflammation with less delayed neurodegeneration to effect and therefore consistent with higher neuronal reserve. Consequently, the treatment effect size for 9-HPT remains constant throughout the OLE (Table 1).

Table 1: Consistency of results across disability outcomes, MRI active

	CDP-24	CDP-12	9-HPT*
Unadjusted: DB Stratified	0.71 (0.47, 1.06)	0.68 (0.46, 0.99)	0.52 (0.32, 0.85)

Unadjusted: OLE Stratified	[redacted]	[redacted]	[redacted]
Main: OLE Stratified Treatment Group RPSFT	[redacted]	[redacted]	[redacted]

DB, double blind; OLE, open label extension; RPSFT, rank preserving structural failure time. * 20% increase in 9-HPT confirmed over 12 weeks. MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Figure 1: Kaplan Meier: CDP-24 in ORATORIO + OLE with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Table 2: Patients at risk: ORATORIO + OLE CDP-24 with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Figure 2: Patients at risk: ORATORIO + OLE CDP-24 with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Figure 3: Kaplan Meier: ORATORIO + OLE CDP-12 with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Table 3: Patients at risk: ORATORIO + OLE CDP-12 with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Figure 4: Patients at risk: ORATORIO + OLE CDP-12 with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Figure 5: Kaplan Meier: ORATORIO + OLE 9-HPT with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Table 4: Patients at risk: ORATORIO + OLE 9-HPT with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Figure 6: Patients at risk: ORATORIO + OLE 9-HPT with RPSFT adjustment (MRI active)

MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Table 5: Sensitivity analyses, MRI active population (MRI active)

	CDP-24	CDP-12	9-HPT*
Main: OLE Stratified Treatment Group RPSFT	[redacted]	[redacted]	[redacted]
Sensitivity 1: OLE Unstratified Treatment Group RPSFT	[redacted]	[redacted]	[redacted]
Sensitivity 2: OLE Stratified On Treatment RPSFT	[redacted]	[redacted]	[redacted]
Sensitivity 3: OLE Stratified Treatment Group RPSFT - 50% efficacy switchers	[redacted]	[redacted]	[redacted]
Sensitivity 4: OLE Stratified Treatment Group RPSFT - 20% efficacy switchers	[redacted]	[redacted]	[redacted]
Sensitivity 4: OLE Stratified Treatment Group RPSFT with recensoring	[redacted]	[redacted]	[redacted]

* 20% increase in 9-HPT confirmed over 12 weeks. MRI Active is defined as >0 T1 Lesion at Baseline or Screening or an increase in T2 Lesions from Screening to Baseline. The 'Treatment Group' approach to RPSFT as described by Latimer et al 2014 was performed. The recensoring algorithm of White et al 1999 was used with all censoring assumed to be administrative. Both unstratified and stratified (Region ROW vs USA and Age >45 vs <=45) log-rank test were used to perform the G-estimation. Estimated RPSFT hazard ratios have the 95% CI inflated using the ITT p-value from G-estimation test.

Results of revised base case

The revised base case incorporates the following changes which reflect the committee's preferences:

- CDP-24 used as the measure for disability progression
- Cost and disutilities of relapses included
- Risk of progressive multifocal leukoencephalopathy (PML) for ocrelizumab included (using data from rituximab in rheumatoid arthritis as proxy, similar to approach in recent NICE appraisal for ocrelizumab in relapsing MS, ID937)
- Utility decrement for fatigue excluded
- 50% waning after 10 years included (uncertainty was highlighted by the committee, concluding that true waning likely lies between an assumption of no waning and an assumption of 50% waning after 5 years. Based on the durability of effect observed in OLE data, we propose that waning is assumed to start after 10 years [in line with recent RRMS MTA TA527], see below)
- UK MS Survey used as the source of EDSS costs (in line with committee's conclusion that EDSS costs are the same in RRMS and PPMS, similar to the approach used in the recent NICE appraisal for ocrelizumab in relapsing MS, ID937)
- Stopping rule of EDSS ≥7 used (in line with Roche's understanding of the ACD, uncertainty highlighted by the committee)
- 50% increased stopping rates after 5 years used, as proposed by the ERG (uncertainty highlighted by the committee)

However, Roche believe that several conclusions in the ACD are not a reasonable and equitable interpretation of the evidence and encourage the Committee to reconsider its conclusions. Please refer to the responses provided by Roche. As such, the revised base case includes the following modelling assumptions preferred by Roche:

- CDP-24 effect size from crossover adjustment of OLE (new evidence)
- Health state utility values from ORATORIO study used to reflect the population with early PPMS with inflammatory activity
- Utility decrements for upper limb impairment included

The impact of some of these assumptions and inputs is explored further in scenario analyses.

Base case results

The economic analysis indicates that [redacted] QALYs are accrued over a lifetime with ocrelizumab treatment, compared with [redacted] QALYs with BSC. The main benefit of disease modifying treatment is not in extending life but in improving the quality of life, as expressed by the incremental QALY gain of 0.95 (i.e. 11 months of perfect health).

The base case analysis indicates an ICER of [redacted] at list price and £62,766 at DoH-approved PAS price, respectively (Table 6 and Table 7), without consideration of the proposed commercial offer for PPMS.

Sensitivity analysis

Deterministic sensitivity analysis

For one-way sensitivity analysis parameters were varied between the lower and upper boundary of the 95% confidence/credible interval or by 20% of the mean if a distribution was not available (values available in cost-effectiveness model). The ten parameters most sensitive to change were included in the tornado diagrams (Figure 7 and Figure 8).

Results were most sensitive to changes in the treatment effect on confirmed disability progression, discount rate for costs and effects, and cost of EDSS health states, which is to be expected for a chronic disease such as PPMS in which the costs and benefits are accrued over a lifetime. Variation in the cost of drug administration in years 2+ and disutillity for upper limb impairment also influenced cost-effectiveness results, but to a lesser degree.

Other parameters had relatively little impact on the overall results.

Probabilistic sensitivity analysis

All model variables that had a distribution assigned were presented in company submission table 62. Probabilistic sensitivity analysis was conducted with 1,000 iterations to determine the uncertainty surrounding the base-case ICERs.

The probabilistic results are broadly similar - albeit higher – than the deterministic results, lending support to the overall conclusions (Table 8 and Table 9).

At list price or DoH-approved PAS price there is 0% probability that ocrelizumab is effective at a £30k ICER threshold (Figure 9 and

Figure 12), without consideration of the proposed commercial offer for PPMS.

The incremental cost-effectiveness planes indicate that ocrelizumab is mostly situated in the north-east quadrant, meaning it is more efficacious and costlier than BSC. Most of the simulations are located above the ICER threshold of £30,000 per QALY at list price or the DoH-approved PAS price (Figure 11 and Figure 14).

Scenario analysis

Scenario analysis was performed to test the sensitivity of the economic model to different model assumptions or input sources (Table 10 and Table 11). The base case results can be considered conservative compared with the natural history scenarios which all improved the ICER. Results were particularly sensitive to the source of efficacy. Application of recent datacuts with longer follow up from the open label extension study improve the cost-effectiveness of ocrelizumab. In addition, source of health state utilities values and impact of upper limb function were key drivers of the model.

Finally, the results were sensitive to clinical uncertainties highlighted by the committee in the ACD, i.e. waning assumption and treatment duration. As described in our response to ACD, we consider the ERG scenario of 50% waning after 5 years to be implausible in light of the sustained effect of ocrelizumab in the open label extension study. There was insufficient time to update the model for ACD response with extrapolations for all-cause discontinuation based on the latest OLE datacut. However, the extrapolations based on the previous datacut highlighted that Gompertz, exponential, and Weibull distributions provided the best statistical fit. Application of Loglogistic and Lognormal distributions (combined with EDSS ≥7 stopping rule) resulted in predicted average treatment durations of nearly 8-9 years which clinical expert advice considered to be too long.

Table 6: Incremental analysis, revised base case MRI active (based on ocrelizumab list price)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Incremental analysis, revised base case MRI active (based on ocrelizumab PAS)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,766	62,766

Table 8: Probabilistic results, revised base case MRI active (based on ocrelizumab list price)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: Probabilistic results, revised base case MRI active (based on ocrelizumab PAS)

Technologies	Mean costs (£)	Mean QALYs	Incremental mean costs	Incremental mean QALYs	Probabilistic ICER versus baseline	Incremental probabilistic ICER
BSC	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	67,336	67,336

Figure 7: One way sensitivity analysis for ocrelizumab versus BSC (NMB, list price)

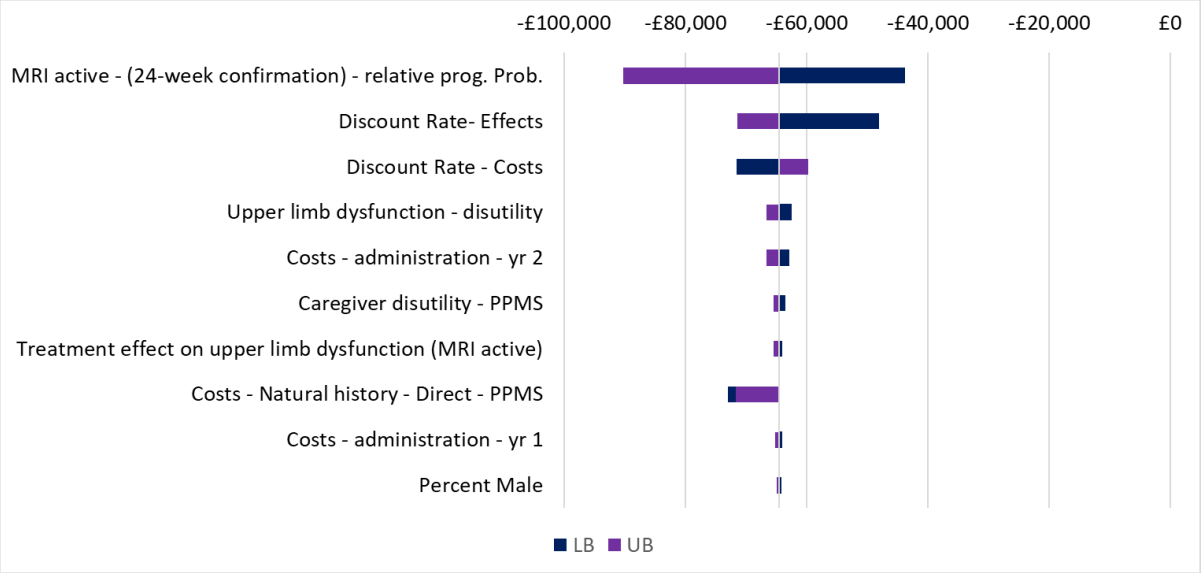

Figure 8: One way sensitivity analysis for ocrelizumab versus BSC (NMB, PAS price)

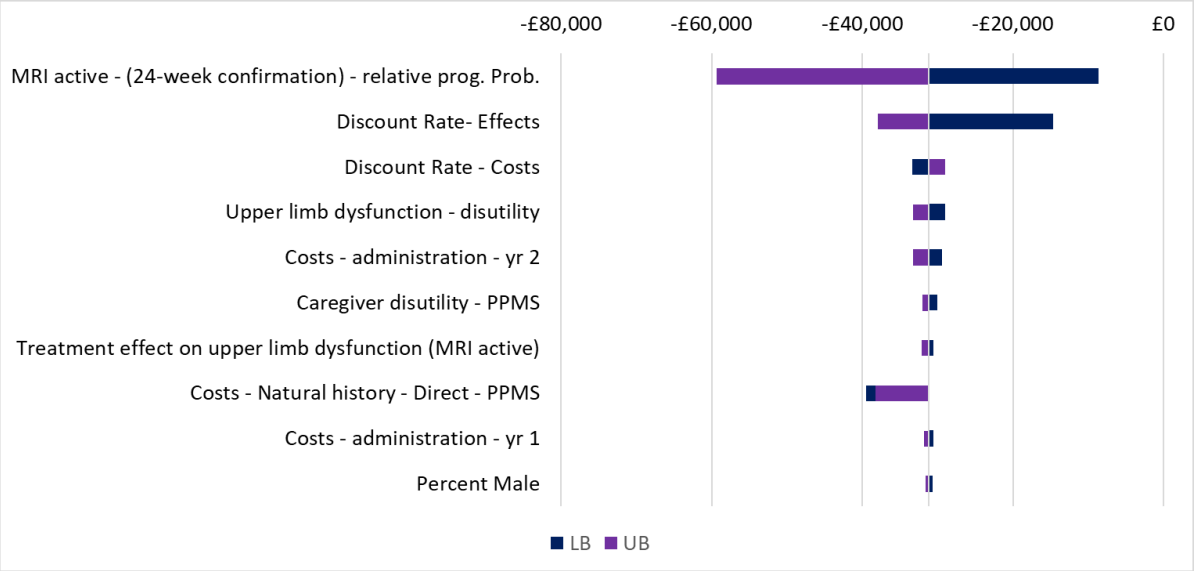

Figure 9: Cost-effectiveness acceptability curve for ocrelizumab and BSC (list price)

Figure 10: Cost-effectiveness plane for ocrelizumab and BSC (list price)

Figure 11: Incremental Cost-effectiveness Plane for ocrelizumab versus BSC (list price)

Figure 12: Cost-effectiveness acceptability curve for ocrelizumab and BSC (PAS price)

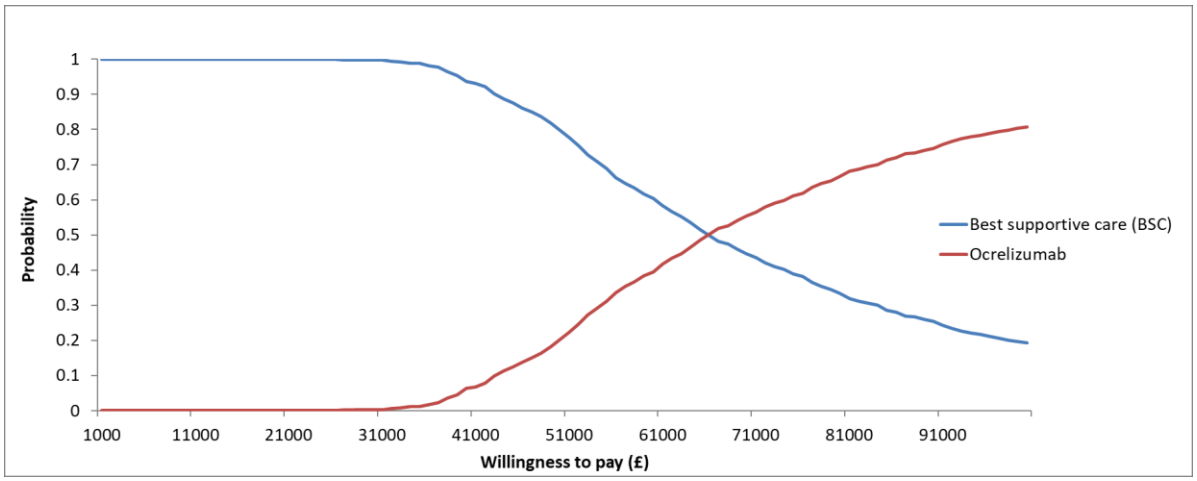

Figure 13: Cost-effectiveness plane for ocrelizumab and BSC (PAS price)

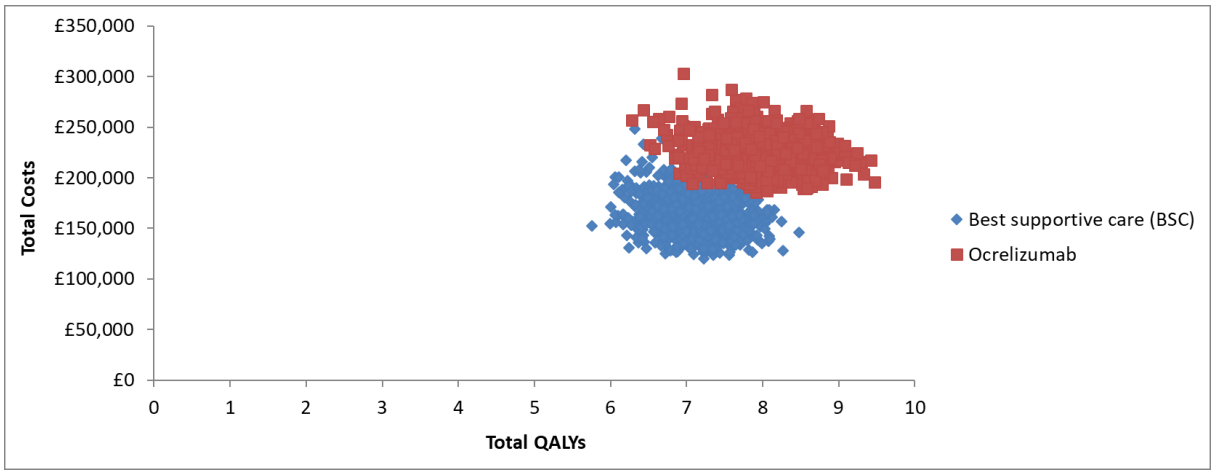

Figure 14: Incremental Cost-effectiveness Plane for ocrelizumab versus BSC (PAS price)

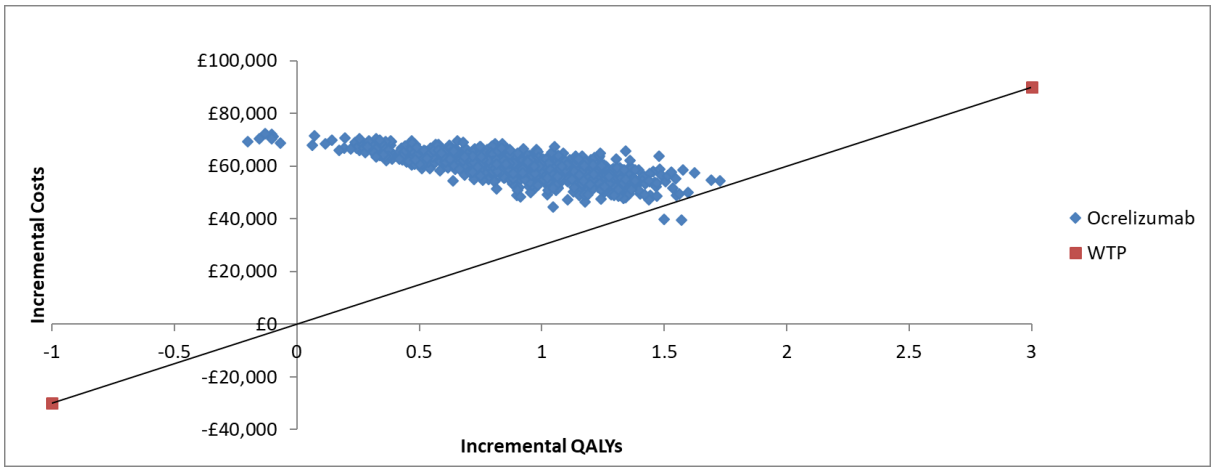

Table 10: Results of scenario analysis in MRI active population, based on list price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case MRI active	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history					
Acceleration factor set to 1.05 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acceleration factor set to 1.1 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy					
Efficacy set to CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORATORIO + OLE unadjusted CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORATORIO CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORATORIO + OLE unadjusted CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORATORIO CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No waning assumed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs					
Gompertz extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule set to EDSS 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities					

Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Include fatigue impact in model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Results of scenario analysis in MRI active population, based on PAS price

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case MRI active	[redacted]	[redacted]	[redacted]	[redacted]	£62,766
Natural history					
Acceleration factor set to 1.05 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	£60,015
Acceleration factor set to 1.1 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	£57,555
Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	£50,396
Efficacy					
Efficacy set to CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£66,941
ORATORIO + OLE unadjusted CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£76,673
ORATORIO CDP-12 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£82,389
ORATORIO + OLE unadjusted CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£71,553
ORATORIO CDP-24 (MRI active)	[redacted]	[redacted]	[redacted]	[redacted]	£92,331
No waning assumed	[redacted]	[redacted]	[redacted]	[redacted]	£59,079
Costs					
Gompertz extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	£66,354
Exponential extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	£71,931
Weibull extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	£72,316
Loglogistic extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	£74,896

Lognormal extrapolation of discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	£78,469
Stopping rule set to EDSS 8	[redacted]	[redacted]	[redacted]	[redacted]	£63,592
Stopping rule set to EDSS 9	[redacted]	[redacted]	[redacted]	[redacted]	£65,439
Utilities					
Exclude upper limb impairment from model	[redacted]	[redacted]	[redacted]	[redacted]	£69,282
Include fatigue impact in model	[redacted]	[redacted]	[redacted]	[redacted]	£58,154
Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	£69,318

References

1. Latimer NR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching 2014 [Available from: http://www.nicedsu.org.uk/TSD16_Treatment_Switching.pdf.
2. National Institute for Health and Care Excellence. Beta interferon and glatiramer acetate for treating multiple sclerosis (review of TA32) [ID809] 2018.
3. Latimer NR, White IR, Abrams KR, Siebert U. Causal inference for long-term survival in randomised trials with treatment switching: Should re-censoring be applied when estimating counterfactual survival times? Stat Methods Med Res. 2018:962280218780856.
4. Tur C, Montalban X, Tintore M, Nos C, Rio J, Aymerich FX, et al. Interferon beta-1b for the treatment of primary progressive multiple sclerosis: five-year clinical trial follow-up. Arch Neurol. 2011;68(11):1421-7.
5. Giovannoni G, Cutter G, Sormani MP, Belachew S, Hyde R, Koendgen H, et al. Is multiple sclerosis a length-dependent central axonopathy? The case for therapeutic lag and the asynchronous progressive MS hypotheses. Mult Scler Relat Disord. 2017;12:70-8.
6. Krieger SC, Sumowski J. New Insights into Multiple Sclerosis Clinical Course from the Topographical Model and Functional Reserve. Neurologic clinics. 2018;36(1):13-25.
7. Sandroff BM, Schwartz CE, DeLuca J. Measurement and maintenance of reserve in multiple sclerosis. J Neurol. 2016;263(11):2158-69.
8. Sumowski JF, Rocca MA, Leavitt VM, Meani A, Mesaros S, Drulovic J, et al. Brain reserve against physical disability progression over 5 years in multiple sclerosis. Neurology. 2016;86(21):2006-9.
9. Weier K, Mazraeh J, Naegelin Y, Thoeni A, Hirsch JG, Fabbro T, et al. Biplanar MRI for the assessment of the spinal cord in multiple sclerosis. Mult Scler. 2012;18(11):1560-9.

Ocrelizumab for treating primary progressive multiple sclerosis [ID 938] – Addendum 3 of the ERG report

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows

Ocrelizumab for treating primary progressive multiple sclerosis, Warwick Evidence, 2018

Contributions of authors:

Peter Auguste (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Jill Colquitt (Senior Researcher) co-ordinated and conducted the critique of the clinical effectiveness evidence; Martin Connock (Senior Research Fellow) reviewed and critiqued the survival analysis and cost-effectiveness evidence and undertook additional analyses; Emma Loveman (Senior Researcher) conducted the critique of clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Olga Ciccarelli (Clinical Professor) provided expert clinical advice; Carl Counsell (Reader) provided expert clinical advice; Xavier Armoiry (Senior Research Fellow) co-ordinated the project and the report, and reviewed and critiqued the clinical effectiveness evidence.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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1. New analyses presented by the Company

The ERG has reviewed the new analyses provided by the Company following the publication of the Appraisal Consultation Document (ACD) which was issued after the first meeting of the appraisal committee.

We welcome the following changes made by Roche in their revised base-case:

- Use of confirmed disability progression for 24 weeks (CDP-24) instead of CDP-12
- Inclusion of costs and disutilities of relapses
- Use of UK MS Survey as the source of EDSS costs
- Exclusion of utility decrement for fatigue

We have noted:

- The inclusion in the model of the risk of progressive multifocal leukoencephalopathy (PML) which is consistent with the approach taking for ocrelizumab in RRMS.
- The use of a stopping rule of EDSS≥7 as opposed to EDSS≥8 in the original submission.

The ERG believes these two changes to be reasonable.

Below, we have reported a number of specific comments regarding assumptions that the Company retained from the original submission together with other changes made by the Company, this also includes concerns on changes made and not emphasised by the Company in their response document.

1.1. New evidence regarding the treatment effect size

In the original submission, the company presented post-hoc analyses based on an extended controlled treatment period that added approximately 3 months of controlled follow-up. The additional period went from the clinical cut-off date (24 July 2015) to 20 January 2016 or the time when the patient received their first open-label dose of ocrelizumab, whichever came first. During this time, patients were gradually unblinded and switched to open-label extension.

Here, the Company has presented more mature data from the open-label extension study with the most recent data cut-off extended to Week 336 (5th February 2018).

In our original report, we indicated that we were interested in results reporting slightly more mature data but also that we were cautious regarding these additional results given that some patients were

unblinded over the extended controlled treatment period, meaning results are more at risk of performance bias.

Although we appreciate the efforts made by the Company to provide more mature data from the OLE study, our original concerns regarding the risk of performance bias apply here to a greater extent since all patients in the ocrelizumab arm were eventually aware of their treatment allocation. There is also the potential for detection bias as outcome assessors may have become aware of the treatment allocation.

We have noted that in the original submission the Company preferred to use the effectiveness estimates from the double blind period over those from the extended controlled treatment period. Conversely, the Company has chosen to use in its revised base-case the estimates from the OLE study. While we appreciate OLE study estimates may seem more mature compared to those from the double-blind period, we believe these to be at much higher risk of bias.

Following the double-blind period, nearly all patients chose to enter the OLE study. To account for patients initially enrolled in the placebo that switched to ocrelizumab, the Company has considered DSU-recommended methods to adjust for patient cross-over, of which the rank preserving structural failure time (RPSFT) model was eventually chosen by the Company.

The Company has indicated that this methodology has been used in many previous oncology NICE appraisals together within the recent RRMS appraisal on beta-interferon and glatiramer acetate. While the ERG agrees with the company's statement regarding cancer drugs appraisals, it is unclear to the ERG what is the company is referring to regarding the MS MTA.

In the study protocol of the ORATORIO RCT, it was stated that data from the OLE study "[redacted]". The SAP provided by the Company within the study report was related to primary analyses (i.e. those from the double-blind period) but not to the OLE study. An urgent request was made by the ERG to obtain the SAP related to the OLE to check whether the analyses provided by the Company regarding the OLE study were pre-specified but due to time constraints no response was obtained at the time of submission of addendum 3. It is therefore unclear to the ERG whether these analyses were pre-specified or undertaken post-hoc.

Consistent with our original report, we have chosen to keep using the effectiveness estimates from the double-blind period in our base-case rather than those from the OLE study which have been used in sensitivity analyses.

The ERG did not have access to individual-patient data and due to time constraints did not request to access to these data to double-check the validity of findings after adjustment for cross-over with the RPSFT method.

However, the estimated effect size after adjustment seems plausible compared to the unadjusted one. In the sensitivity analysis pertaining to the effect size, the ERG has preferred to use the cross-over adjusted estimate.

The Company has presented the results from the OLE study as evidence that the treatment effect is sustained up to 6 ½ years.

Despite the risk of performance bias previously emphasised regarding the OLE study, we have noted on the Kaplan Meir curves that there was no apparent sign of effect waning up to the end of observation period of the OLE study (6 ½ years) and have therefore considered this represented reasonable evidence to support the absence of waning effect from five years as in our original ERG's preferred base-case. However, there is still considerable uncertainty in a longer-term perspective.

We have therefore decided to revise our base-case with a starting point of our waning effect model from 7 years, date at which data are extrapolated.

1.2. Inclusion of utility decrements for the upper limb impairment

The Company has maintained its position regarding the inclusion of utility decrements related to upper limb impairment.

The ERG are unconvinced that the Company has not provided any further valid reason to support the inclusion of the utility decrements related to upper limb impairment.

In the ERG original report, we have extensively reviewed the inclusion of utility decrements related to upper limb impairment and we fully retain our original concerns.

The ERG would like to add that the two independent clinical experts who attended the appraisal committee meeting have indicated that the 9 hole-peg test (9-HPT), which is the surrogate outcome taken by the Company to reflect upper limb impairment, is very marginally used within the NHS.

Last, the ERG recalls that a number of comments were made in our report regarding the unclear effect of ocrelizumab on functional outcomes other than EDSS. In particular, we commented that "the

company chose results for a 20% increase in 9-HPT to reflect upper limb function impairment suggesting this corresponds to clinically meaningful upper limb impairment but made no statement on 1) the fact that MSFC is a composite outcome that includes the 9-HPT; 2) why MSFC outcomes showed no differences between treatments arms". We note that the Company has not responded to these originally stated concerns.

In conclusion, the ERG has provided its revised base-case which still excludes utility decrements related to upper limb impairment.

1.3. Duration of effect and discontinuation rate

We appreciate that the Company has now considered a 50% waning of the effect after 10 years which was not the case in the original submission. The Company has stated the OLE study with nearly 6 ½ years of follow-up has provided evidence that there is no waning of the effect up to this time point. Most importantly, we have noted that the Company has increased stopping rates to 50% after 5 years. The statement made by the Company that this 50% increased stopping rates after 5 years is "as proposed by the ERG" is misleading. Indeed, in our original report, we have clearly indicated (page 94 ERG report) that we felt "the most relevant way to apply a waning of treatment effect is to increase the HR for CDP over time while increasing the rate of discontinuation to treatment as a consequence of an objective loss of effectiveness". This means we have linked the increase of the HR and the rate of discontinuation to treatment.

Consequently, there is no consistency in the proposition by the Company to apply a waning of the effect after 10 years while increasing stopping rates after 5 years.

Should any increase of stopping rates be applied, this should be done from the same point of the waning of the effect.

Given that we have in our revised base-case applied a waning effect from 7 years on, we have applied a 50% increase of stopping rates from 7 years. This was done by halving the time spent "in treatment" from 7 years onward using the Gompertz model of discontinuation.

Last, we have noted that the 50% increased rates used by the Company in its revised base-case are not those we reported the use of in the addendum 1 of our original report. The discrepancy between these two set of values are illustrated in

Table ***1***. While the Company derived its annual discontinuations rates multiplying the original values by 1.5 from X time onwards, the ERG has derived its original values by halving the time spent "in treatment" from 5 years onward using the Gompertz model of discontinuation; this method more explicitly takes into account the modelled extrapolation beyond the observed data.

Table 1: Annual discontinuation rate used in Evidence review group's base-case compared to those from the Company

Year	Annual discontinuation		
	Company original submission	**ERG values (addendum 1 of ERG report)**	**Company new analyses (post-ACD)**
1	[redacted]	6.50%	[redacted]
2	[redacted]	7.07%	[redacted]
3	[redacted]	7.69%	[redacted]
4	[redacted]	8.35%	[redacted]
5	[redacted]	9.10%	[redacted]
6	[redacted]	25.19%	[redacted]
7	[redacted]	27.13%	[redacted]
8	[redacted]	29.19%	[redacted]
9	[redacted]	31.37%	[redacted]
10+	[redacted]	33.68%	[redacted]

1.4. Non-medical direct costs

The ERG noted that in the revised model submitted, the company's analyses are based on the exclusion of non-medical direct costs, with no justification provided about why these costs had been excluded. In scenario analysis of the company's base-case, the ERG have included these costs, whilst holding all other inputs fixed to assess the impact to the ICER. Our base-case results include these non-medical direct costs.

2. Company's base case and probabilistic results

In this section, the ERG has reported results from the Company's base case **using the agreed PAS price** (i.e. analyses based on the list price were not presented).

Table 2: Deterministic results, company base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	62,800
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 3: Probabilistic sensitivity analysis, company base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	67,300
ICER, incremental life years gained; QALY, quality adjusted life years gained					

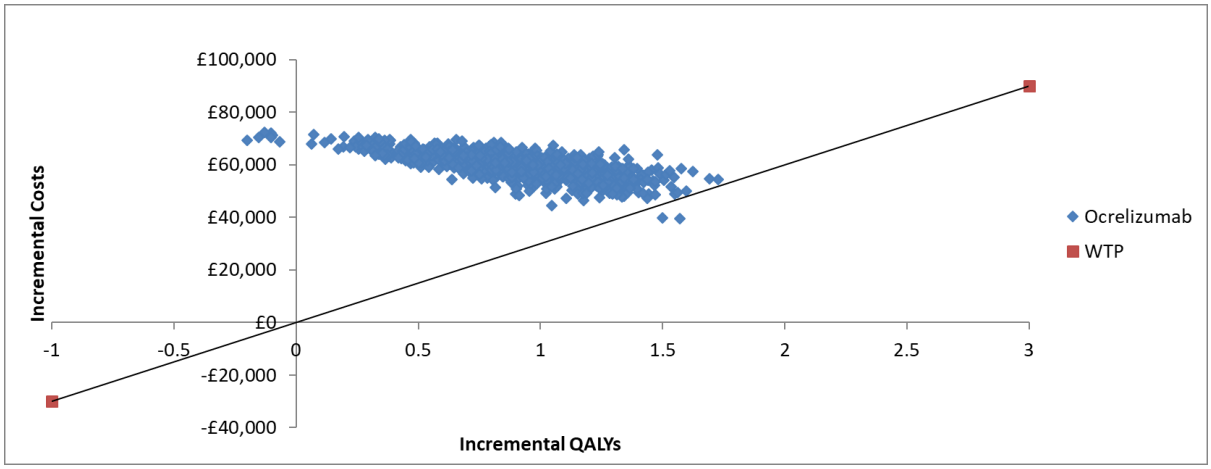

Figure 1: Cost-effectiveness plane, company base case

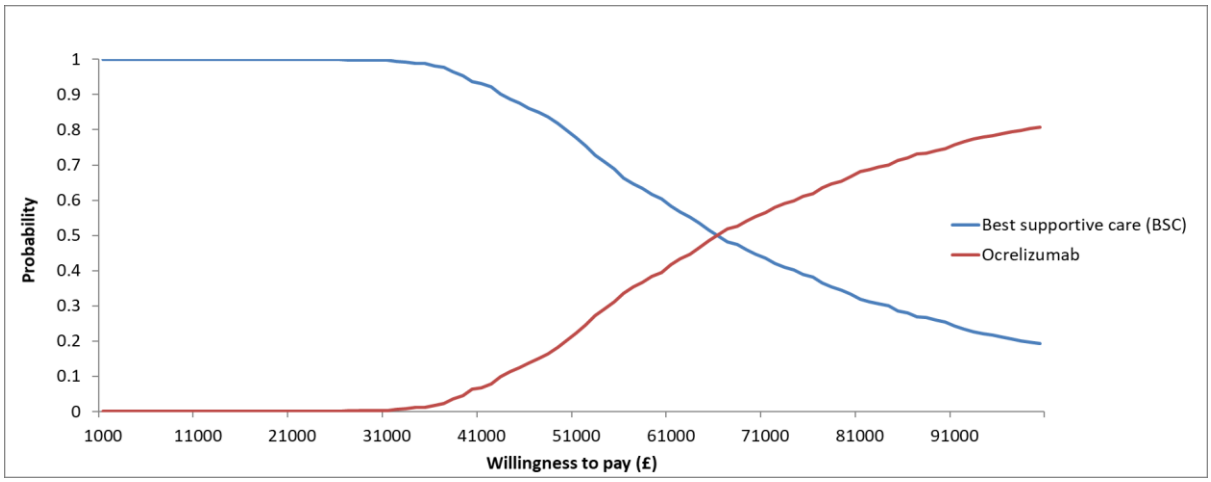

Figure 2: Cost-effectiveness acceptability curve, company base case

3. Exploratory and sensitivity analyses undertaken by the ERG

As in section 2, the ERG has reported analyses **using the agreed PAS price** (i.e. analyses based on the list price were not presented).

3.1. ERG's individual parameter changes to the Company's base-case

Based on the ERG's concerns, we have used a modified version of the company's base-case model to undertake exploratory analyses, by incorporating the following changes/assumptions:

- SA1: Efficacy set to CDP-24 for the unextended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)
- SA2: 50% decrease in the effectiveness from 7 years onwards and an increase in annual discontinuation rate from 7 years onwards such that the average time spent in treatment beyond 7 years was reduced to 50%
- SA3: Excluding utility decrements for upper limb impairment
- SA4**:** Including non-medical direct costs

In our exploratory analyses we present the results based on each change made.

SA1: Efficacy set to CDP-24 for un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)

Table 4: Deterministic results, SA1 from Company's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	92,300
ICER, incremental life years gained; QALY, quality adjusted life years gained					

SA2: 50% decrease in the effectiveness from 7 years onwards and an increase in annual discontinuation rate from 7 years

The ERG undertook a scenario analysis assuming an increase in the annual discontinuation rate such that the average time spent in treatment beyond 7 years was reduced to 50%. The effect of applying this correction in discontinuation trajectory is illustrated in Figure 3.

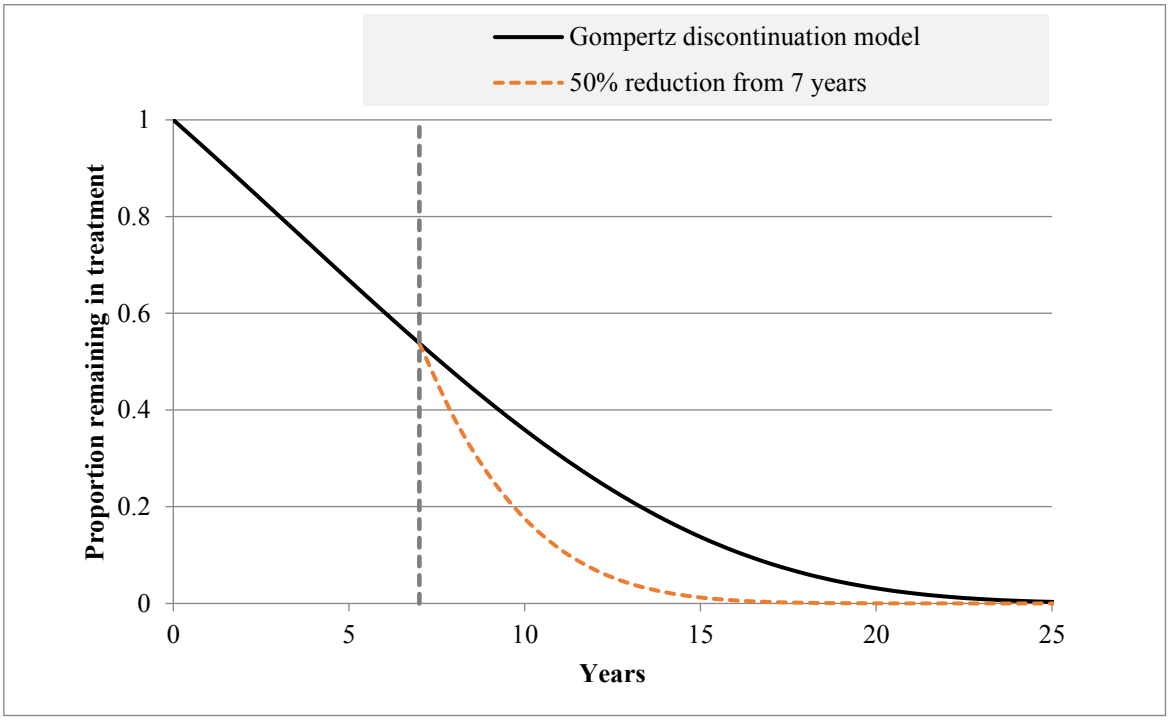

Figure 3: Illustration of the scenario assuming an increase in the annual discontinuation rate such that the average time spent in treatment beyond 7 years is reduced to 50%

In Table 5, we report the ERG values for annual discontinuation rate to be used in the company's model derived from Figure 1 together with those for annual discontinuations rates obtained using the same method but beyond 5 years (as in the original ERG report) . Applying an annual discontinuation rate based on a 50% decrease in time spent in treatment from 10 years onwards would provide the same rate at year 10 as when there is no increased discontinuation; this is because the rates that change are years subsequent to year 10 (i.e. year 11, 12 etc). Though not explicitly stated, the company's economic model assumes that at and after year 10 the annual discontinuation is the same at all years from and including year 10 (all years 10 and beyond).

Table 5: Annual probability of discontinuation

Year	Discontinuation		
	No increase in discontinuation (*original company submission*)	**50% increase from 5 years (*ERG original base-case/ ERG revised sensitivity analysis*)**	**50% increase from 7 years (*ERG revised base case*)**
1	[redacted]	6.50%	6.50%
2	[redacted]	7.07%	7.07%
3	[redacted]	7.69%	7.68%
4	[redacted]	8.35%	8.35%
5	[redacted]	9.10%	9.07%
6	[redacted]	25.19%	9.86%
7	[redacted]	27.13%	10.73%
8	[redacted]	29.19%	28.95%
9	[redacted]	31.37%	31.12%
10+	[redacted]	33.68%	33.41%

Table 6: Deterministic results, SA2 from Company's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	67,400
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Applying a treatment waning effect and an increase in annual discontinuation resulted in an ICER of approximately [redacted] per QALY gained (see Table 6).

SA3: Excluding utility decrements for upper limb impairment

Table 7: Deterministic results, SA3 from Company's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	69,300
ICER, incremental life years gained; QALY, quality adjusted life years gained					

- **SA4: Including non-medical direct costs**

Table 8: Deterministic results, SA4 from Company's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	60,300
ICER, incremental life years gained; QALY, quality adjusted life years gained					

→ Scenario analysis results

Table 9: Scenario analysis results based on individual changes made to company's base-case

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
Company's base-case results	[redacted]	[redacted]	[redacted]	62,800	/
Scenario analyses undertaken by the ERG					
Trial data (ORATORIO)	[redacted]	[redacted]	[redacted]	92,300	+29,500
Waning from 7 years and increase in annual discontinuation rate from 7 years	[redacted]	[redacted]	[redacted]	67,400	+4600
Excluding utility decrements for upper limb impairment*	[redacted]	[redacted]	[redacted]	69,300	+6500
Including non-medical direct costs	[redacted]	[redacted]	[redacted]	60,300	-2500
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained					

In Table 9, using the hazard ratio which is based on the double blind period of the ORATORIO trial data had the greatest impact to the company's base-case, with an increase from approximately £62,800 to £92,300 per QALY gained.

3.2. ERG's preferred base case and sensitivity analyses

The ERG preferred base-case includes the following changes:

- Efficacy set to CDP-24 for un-extended treatment controlled period (minimum of 120 weeks of double-blinded controlled period)
- 50% decrease in treatment efficacy from 7 years onwards and an increase in annual discontinuation rate from active treatment such that the average time spent in treatment beyond 7 years was reduced to 50%
- Excluding utility decrements for upper limb impairment
- Excluding utility decrements for fatigue
- Including non-medical direct costs
- Including costs, disutilities, and treatment effect associated with relapses
- Using utility values reported by Orme et al. (2007)
- Stopping rule from EDSS ≥7

3.2.1. Base case deterministic results and probabilistic sensitivity analysis:

Results in Table 10 show that ocrelizumab is expected to cost approximately [redacted] more than BSC and expected to yield [redacted] QALYs, with an ICER of approximately £130,300 per QALY gained. The ICER based on the probabilistic results (Table 11) is higher than the ICER based on the deterministic results. The discrepancy arises as the PSA provides a lower average incremental QALY estimate, although the cause of this is uncertain.

Table 10: Deterministic results, ERG base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	130,300
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Table 11: Probabilistic sensitivity analysis, ERG base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	136,500
ICER, incremental life years gained; QALY, quality adjusted life years gained					

Results for 1000 runs of the Monte Carlo simulation (see Figure 4) show considerable uncertainty about the incremental QALYs, and less so for the incremental costs. Figure 5 shows the results of the probabilistic sensitivity analysis presented in the form of cost-effectiveness acceptability curve for the comparison between ocrelizumab and BSC. At a WTP threshold of £30,000 per QALY, 0% of the simulations were below this threshold. It should also be noted that a proportion of simulations are in the north-west quadrant, which signifies that BSC dominated treatment with ocrelizumab.

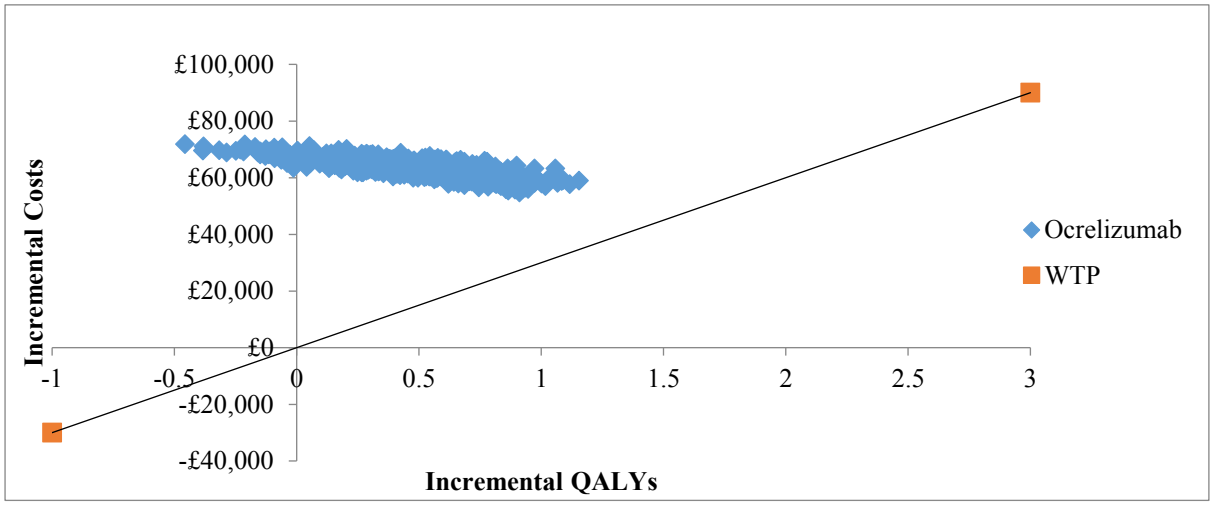

Figure 4: Cost-effectiveness plane, ERG base-case

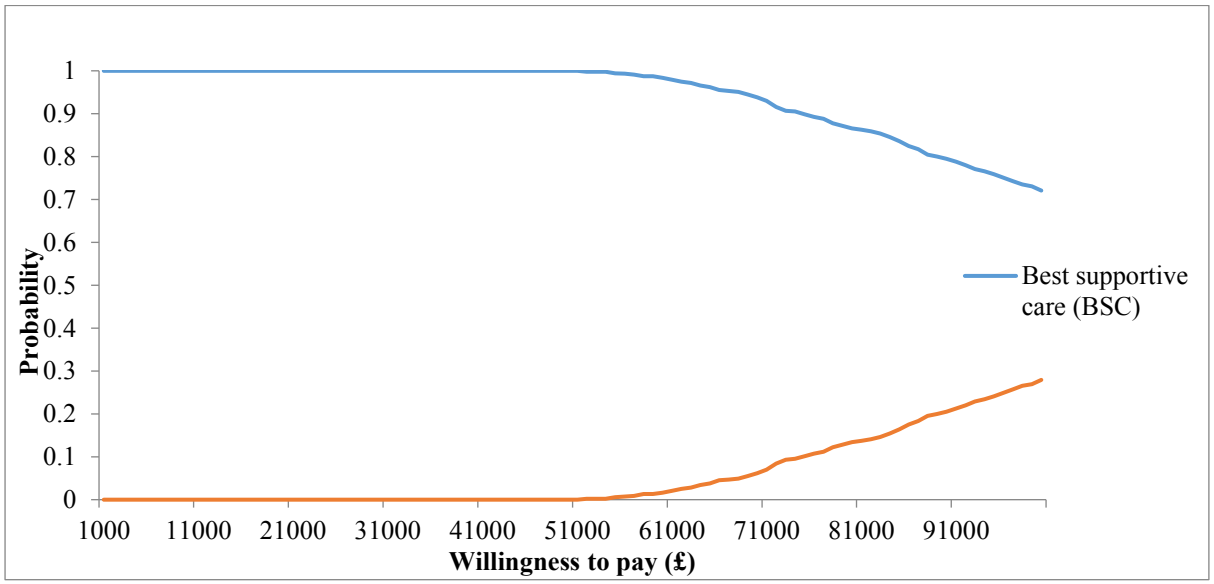

Figure 5: Cost-effectiveness acceptability curve, ERG base case

3.2.2. ERG's sensitivity analyses

We further undertook scenario analyses using our base-case model:

- SA1: Efficacy set to CDP-24 for extended treatment controlled period (open-label study) using the adjusted effectiveness estimate
- SA2: Waning from 5 years and increase in annual discontinuation rate such that the average time spent in treatment beyond 5 years was reduced to 50%
- SA3: Using utility values according to the ORATORIO RCT
- SA4: Inclusion of utility decrements for upper limb function
- SA5: Stopping rule from EDSS ≥8

SA1: Efficacy set to CDP-24 for extended treatment controlled period (open-label study) using the adjusted effectiveness estimate

Table 12: Deterministic results, SA1 from the ERG's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	88,900
ICER, incremental life years gained; QALY, quality adjusted life years gained					

SA2: Waning from 5 years and increase in annual discontinuation rate such that the average time spent in treatment beyond 5 years was reduced to 50%

Table 13: Deterministic results, SA2 from the ERG's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	141,200
ICER, incremental life years gained; QALY, quality adjusted life years gained					

SA3: Using utility values according to the ORATORIO RCT

Table 14: Deterministic results, SA3 from the ERG's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	116,300
ICER, incremental life years gained; QALY, quality adjusted life years gained					

SA4: Inclusion of utility decrements for upper limb function

Table 15: Deterministic results, SA4 from the ERG's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	113,700
ICER, incremental life years gained; QALY, quality adjusted life years gained					

SA5: Stopping rule from EDSS ≥8

Table 16: Deterministic results, SA5 from the ERG's base case

Strategy	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	-
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	135,500
ICER, incremental life years gained; QALY, quality adjusted life years gained					

→ Scenario analysis results

In Table 17, we have summarised the scenario analysis results undertaken on our preferred base-case. These results show the impact of each change to our preferred base-case ICER while all other inputs/assumptions remain constant. Using the hazard ratio based on OLE study after adjustment for cross-over had the greatest impact to our ICER, with a reduction from approximately £130,300 to £88,900 per QALY gained.

Table 17: Scenario analysis results based on individual changes made to ERG base-case

Model inputs	Incremental costs	Incremental QALYs	Incremental LYGs	ICER (cost per QALY)	Impact on the ICER
ERG base-case results	[redacted]	[redacted]	[redacted]	130,300	-
Scenario analyses undertaken by the ERG					
Open-label extension (RPSFT)	[redacted]	[redacted]	[redacted]	88,900	-41,400
Waning from 5 years and increase in annual discontinuation rate from 5 years	[redacted]	[redacted]	[redacted]	141,200	+10,900
Utility values from ORATORIO trial	[redacted]	[redacted]	[redacted]	116,300	-14,000
Including utility decrements for upper limb impairment*	[redacted]	[redacted]	[redacted]	113,700	-16,600
Stopping rule from EDSS ≥8	[redacted]	[redacted]	[redacted]	135,500	+5,200

CDP, confirmed disability progression; CS, company submission; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life years gained; RPSFT, rank-preserving structure failure time
* this scenario analysis also includes the use of an imputed relative risk for 20% increase in 9-HPT